Cheryl 111-10600

Patent
Attorney's Docket No. 010095-003d

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of

Braham Shroot, et al

U.S. Patent No.: RE 34,440 -07/913,891

Reissued: November 9, 1993

For: BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS

Attn: Box Patent Extension

Issued as U.S. Patent No. 5,098,895 on March 24, 1992

APPLICATION FOR EXTENSION OF PATENT TERM

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This application is submitted by including an original, a certified copy and three working copies.

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.710 *et. seq.*, the owner of record of U.S. Patent No. Re. 34,440 ("the '440 Patent"), requests that the term of the '440 Patent be extended 433 days to expire on May 31, 2010. The '440 Patent originally issued on March 24, 1992, as U.S. Patent No. 5,098,895, and was reissued on November 9, 1988, and would in view of GATT, and in the absence of an extended term, expire on March 24, 2009. The named inventors are Braham Shroot, Jacques Eastache and Jean-Michel Bernardos. The patent is assigned of record to Centre

International de Recherches Dermatologiques ("CIRD"), Valbonne, France. The patent is licensed to Galderma Laboratories, Inc., who was the marketing applicant for the NDA for DIFFERIN Gel, 0.1%. As background, Centre International de Recherches Dermatologiques (CIRD) and Galderma Laboratories, Inc. are both organizations existing under the joint ownership of Nestlé S.A. and L'Oréal.

The items required by 37 C.F.R. §1.740(a) follow in §§ I-XVII.

I. APPROVED PRODUCT

The approved product, having the tradename "DIFFERIN Topical Gel, 0.1%", is a topical gel dosage form containing adapalene. Each milliliter (ml) of DIFFERIN Gel contains adapalene 0.1% (1 mg), in a vehicle consisting of propylene glycol, carbomer 940, poloxamer 182, edetate disodium, methylparaben, sodium hydroxide, and purified water. The gel may contain hydrochloric acid to adjust the pH. Specifically, DIFFERIN contains, per g, the following ingredients:

Ingredient	per g	percent (w/w%)
adapalene	1 mg	0.1%
carbomer 940, NF	10 mg	1.0%
propylene glycol, USP	40 mg	4.0%
poloxamer 182	2 mg	0.2%
edetate disodium, USP	1 mg	0.1%
methylparaben, MJ	1 mg	0.1%
sodium hydroxide, NF and/or hydrochloric acid, NF	QS to pH 4.5-6.0	QS to pH 4.5-6.0
purified water, USP	QS to 1 g	QS to 100%

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. The molecular formula is $C_{28}H_{28}O_3$ and the molecular weight is 412.52. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water.

The approved use of DIFFERIN Gel is for the topical treatment of acne vulgaris. Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris.

The approved product is marketed in both a 15 g and a 45 g laminate tube. The gel may be stored at controlled room temperature of 20°-25°C (68°-77°F).

II. APPLICABLE FEDERAL STATUTE

The approved product, DIFFERIN Gel, was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("the Act").

III. PRODUCT APPROVAL DATE

The approved product, DIFFERIN Gel, received permission for commercial marketing or use under Section 505 of the Act on May 31, 1996.

IV. IDENTIFICATION OF DRUG PRODUCT INGREDIENTS

In accordance with 37 C.F.R. §1.740(a)(4), the active ingredient of DIFFERIN Gel is adapalene, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene has not been previously approved for commercial marketing or use under the Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. APPLICATION FILING DEADLINE

The present application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which the application can be submitted is July 29, 1996.

VI. PATENT FOR WHICH EXTENSION IS SOUGHT

The patent for which an extension is being sought is U.S. Patent No. Re. 34,440, which originally issued as U.S. Patent No. 5,098,895 on March 24, 1992, and was reissued on November 9, 1993, in the names of Braham Shroot, Jacques Eustache and Jean-Michel Bernardos. The patent is assigned of record to Centre International de Recherches Dermatologiques (CIRD), Valbonne, France. Since this patent issued before June 8, 1995, the effective date of the Uruguay Round Agreements Act, it is entitled to a patent term of the longer of twenty (20) years from the application filing date or seventeen (17) years from the

patent issue date. For the '440 Patent, a patent term of seventeen (17) years from the patent issue date of March 24, 1992, is longer. The patent would thus expire on March 24, 2009.

VII. COPY OF PATENT

A copy of U.S. Patent No. Re. 34,440 is enclosed herewith as Appendix A, including the entire specification and claims. A copy of the original patent, U.S. Patent No. 5,098,895 is also enclosed in Appendix A.

VIII. COPY OF CERTIFICATE OF CORRECTION, DISCLAIMERS, MAINTENANCE FEE PAYMENT RECEIPTS OR REEXAMINATION CERTIFICATES

There is no certificate of correction, disclaimer or reexamination certificate for this patent. Copies of maintenance fee payment receipts are enclosed in Appendix B.

IX. SHOWING THAT PATENT CLAIMS APPROVED PRODUCT

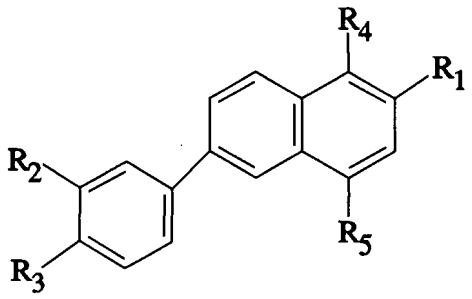
U.S. Patent No. Re. 34,440 claims a process for using the approved DIFFERIN product.

The following patent claim reads directly on the approved product:

Claim 1 reads on the approved product. Claim 1 recites as follows:

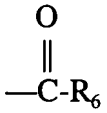
> 1. A process for the treatment of a dermatologic, rheumatismal, respiratory or ophthalmologic disease comprising administering to a person suffering from said disease an effective amount of a composition containing, in

a pharmaceutically acceptable vehicle, as the active ingredient thereof a benzonaphthalene compound of the formula

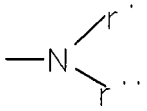


(I)

wherein R_1 represents (I)



or (ii) —CH_2OH,
R_6 represents



or OR_7 wherein R_7 represents hydrogen, alkyl having 1-20 carbon atoms, monohydroxylalkyl or polyhydroxyalkyl, r' and r" represent hydrogen, lower alkyl, mono or polyhydroxyalkyl aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

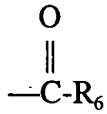
R_2 represents hydrogen, branched or straight chain alkyl 1-15 carbon atoms, alkoxy having 1-4 carbon atoms or a cycloaliphatic radical,

R_3 represents hydrogen, hydroxy, branched or straight chain alkyl having 1-4 carbon atoms, alkoxy having 1-10 carbon atoms, cycloaliphatic radical optionally substituted, a thiocycloaliphatic radical, or —O—$Si(CH_3)_2$—R_8 where R_8 represents linear of branched lower alkyl, provided that at least one of R_2 and R_3 is adamantyl or adamantylthio and

R_4 and R_5 each independently represent hydrogen, lower alkyl, hydroxy or lower acyloxy,

or salt thereof.

Adapalene, having the chemical formula as set forth in Appendix C, is a compound of formula (I), wherein R_1 is



wherein R_6 is OR_7 and R_7 is hydrogen, R_2 is a cycloaliphatic radical, R_3 is an alkoxy having 1-10 carbon atoms, and R_4 and R_5 are each hydrogen. Since DIFFERIN Gel is used for the treatment of a dermatologic disease, i.e., acne vulgaris, and contains adapalene, which is a compound encompassed by the formula of claim 1, claim 1 reads on the approved product.

X. INFORMATION PURSUANT TO 35 U.S.C. §156(g)

The information required by 37 C.F.R. §1.740(a)(10)(v) is set forth below.

An Investigational New Drug (IND) application was filed by Dermatological Products of Texas, Inc. (formerly known as Dermatological Products of Texas, Inc., which company Galderma contracts with for the production and control of drug products under investigational development), for 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid on August 18, 1989, and was received by the FDA on August 21, 1989. The IND became effective on September 20, 1989, thirty (30) days after the date of receipt of the IND. The IND number assigned to 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid was IND 33,540.

A New Drug Application (NDA) was filed by Galderma Laboratories, Inc. (previously known as Owen/Galderma Laboratories, Inc.), on July 15, 1993. The NDA number assigned to the application for DIFFERIN Gel was NDA 20-380. The NDA was approved on May 31, 1996.

Further, the above identified patent is eligible for an extension of patent term, since the following requirements of §156(g) are met:

(1) the above identified patent has not expired prior to the filing of this application for extension of patent term;

(2) the term of the patent has never been extended;

(3) the application for extension of patent term is being submitted by the patent attorney or agent for the owner of record of the above identified U.S. Patent No. RE 34,440 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, who has general authority from said owner to act on behalf of said owner in patent matters including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740;

(4) the product has been subject to a regulatory review period before its commercial marketing or use in the United States;

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first such permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

XI. ACTIVITIES DURING REGULATORY REVIEW PERIOD

Significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to such activities are as follows:

September 19, 1989	Dr. Browder, Mr. Davitt and Dr. Osterberg of FDA met with sponsor representatives to discuss the nonclinical studies planned for submission in support of an NDA.
April 27, 1990	A letter from Dr. Murray Lumpkin in which the agency concurred that the sponsor must provide precautionary labeling clearly stating that there have been positive findings relating to photocarcinogenicity for retinoids and related compounds.
November 7, 1990	A pre-NDA meeting, which included Drs. Lumpkin, Burlington, Evans, Rand, Harkins and Ms. Cook of FDA and sponsor representatives. The focus of the meeting was to review the available clinical data from both U.S. and European studies and to assess the completeness of the clinical evidence of safety and efficacy towards making a determination of fileability of an NDA for the drug product. Based on several comments and concerns expressed by agency participants with regard to the one completed vehicle-controlled study, the sponsor elected to conduct an additional vehicle-controlled study (No. 9104-CD271L-EV), which was initiated in March of 1991, and completed in August of 1991. The submission of the NDA was based on the November 7, 1990 meeting discussions and the completion of the subsequent clinical study.
October 19, 1992	Correspondence to IND 31,997 addressed the matter of submitting "line listings" for patients enrolled in pivotal clinical studies.
July 15, 1993	Original application submission of NDA. The application included the following: **VOLUME 1.1**

ITEM 1. INDEX
ITEM 2. SUMMARY, DRAFT LABELING

VOLUME 1.2 - 1.3

ITEM 3. CHEMISTRY, MANUFACTURING and CONTROLS

VOLUME 1.4

ITEM 4.a. SAMPLES
ITEM 4.b. METHODS VALIDATION

VOLUMES 1.5 - 1.46

ITEM 5. NONCLINICAL PHARMACOLOGY and TOXICOLOGY SECTION

VOLUMES 1.47 - 1.48

ITEM 6. HUMAN PHARMACOKINETICS and BIOAVAILABILITY SECTION

VOLUMES 1.49 - 1.78

ITEM 8. CLINICAL and STATISTICAL DATA SECTION

VOLUMES 1.79 -1.86

ITEM 11. CASE REPORT TABULATIONS

VOLUME 1.87

ITEM 12. CASE REPORT FORMS
STATISTICAL APPENDIX VOLUMES I - VII

July 16, 1993 Desk copies of Volume 1.1 sent to Ms. Rosemary Cook, CSO, FDA.

September 17, 1993 Memo to the file. Filing date confirmed by Ms. Rosemary Cook as September 17, 1993

September 24, 1993 Letter of confirmation to the NDA file of inspection readiness of DPT.

September 24, 1993 Acknowledgment of chemistry deficiencies received September 20 for NDA 20-338 (solution)

December 15, 1993 4-Month Safety Update

December 17, 1993 Amendment for Chemistry, Manufacturing, Controls and Methods Validation

Volume 1 of 2: Description of Methods changes and Specifications for Drug Substance and Drug Product.

Volume 2 of 2: Resubmission of Samples and Methods Validation Package.

March 11, 1994	Submission of statistical tables and SAS Datasets for clinical studies to Dr. Srinivasan (RFD-713)
April 1, 1994	DPT inspection notification. February 22 - March 11, 1994 and March 16 FDA 483. DPT March 29, 1994 response submission.
April 4, 1994	April 1994 - Draft Labeling
April 15, 1994	Statistical review inquiry re: CR89064. Clarification provided by M. Tuley.
April 18, 1994	File memo re: 4/15/94 telephone call from Ms. R. Cook. Biopharmaceutics Review.
April 19, 1994	Commitment to do Phase IV studies. 1) Radiolabel study; 2) *In Vitro* penetration study for establishment of release rate specifications.
April 26, 1994	Submission of FINORGA response to 483
April 26, 1994	Facsimile transmission to R. Cook on status of application
May 20, 1994	Draft Labeling incorporating FDA recommended revisions
May 20, 1994	Facsimile transmission to R. Cook
May 25, 1994	Summary of telephone conversation with R. Cook and Dr. Chambers regarding FDA Draft Labeling.
May 27, 1994	Facsimile transmission to R. Cook
May 24, 1994	FDA Laboratory review comments and recommendations for procedure modifications.
June 3, 1994	Draft Labeling - resubmission (revised - May 1994)
June 6, 1994	Facsimile transmission to R. Cook on status of application.

June 10, 1994	Telephone call to Dr. Dorantes (biopharmaceutics reviewer) regarding submission of Phase IV Study Protocol
June 16, 1994	Submission of: **VOLUME 1 of 3** FINORGA SA May 30, 1994 response to FDA International Technical Operations Branch letter dated May 9, 1994 Applicant responses to FDA Testing Laboratories comments received in a May 24, 1994 FAX **VOLUME 2 of 3** ITEM 4a. - Samples ITEM 4b. - Methods Validation Package - Drug Substance **VOLUME 3 of 3** ITEM 4b. - Methods Validation Package - Drug Product
June 17, 1994	Facsimile transmission to Ms. Rosemary Cook with status of submission amendments.
November 10, 1994	Amendment with FINORGA response to Form 483 September 29-30 inspection observations and CIRD report on identification of M impurity.
January 12, 1995	Facsimile transmission to Ms. R. Cook with amendment summary for status determination.
February 21, 1995	Amendment providing update of foreign approvals and Canadian Product Monograph.
March 14, 1995	Request from Clinical Investigations Branch for Information relating to audit of pivotal studies.
March 16, 1995	Partial response to request for information from the Clinical Investigations Branch.
March 21, 1995	Letter to Rosemary Cook regarding FINORGA reinspection.
March 24, 1995	Notice from FDA Chemist that the third FINORGA reinspection was canceled.

April 4, 1995	Submission of remaining items to Clinical Investigations Branch.
May 1, 1995	CMC Amendment to correct all outstanding deficiencies. Includes request for 3 year expiration dating with data and FINORGA process validation report.
May 10, 1995	Facsimile transmission from J. Timper regarding review of FINORGA DMF update.
July 6, 1995	Patent Information submission per URAA.
August 28, 1995	Summary of FDA audit of Shavin and Lowe sites for clinical study 9105-CD271 G-EV.
September 20, 1995	FDA evaluation of inspection report and documents from the audit of the Lowe Site for: 9105-CD271 G-EV.
October 13, 1995	Track I Export Application to Canada.
December 22, 1995	Facsimile transmission to Ms. Fomaro, DTDP, regarding labeling verbiage.
March 29, 1996	FDA Nomenclature Committee review of DIFFERIN Tradename.
April 12, 1996	Facsimile transmission from Ms. Fomaro - Draft FDA insert labeling.
April 17, 1996	Facsimile transmission to Ms. Fomaro & Mr. Timper re: Description section of insert labeling.
April 22, 1996	Facsimile transmission to Ms. Fomaro re: preclinical issues on data expressions and dose conversions in the carcinogenicity section of insert labeling.
May 1, 1996	Canadian Export Application Approval. Annual Report requirements provided.
May 16,1996	Amendment with documentation from HLS Ltd. supporting preclinical labeling proposal and submission of Draft Insert Labeling (rev. 5/16/96).

May 28, 1996	FDA facsimile transmission of revised draft insert.
May 29,1996	Facsimile transmission to FDA of modified draft insert.
May 29,1996	Facsimile transmission to Ms. Kozma-Fomaro of Draft Insert Labeling Amendment.
May 30, 1996	Amendment with final draft labeling.
May 31, 1996	FDA Approval Letter.

XII. ELIGIBILITY OF PATENT FOR EXTENSION

In the opinion of Applicant, the above identified patent is eligible for an extension of the term to expire May 31, 2010. The length of the claimed extension was determined by Applicant, pursuant to 37 C.F.R. §1.775, to be 433 days, which is fourteen years from the date of the FDA final approval, as described below:

A. Length of the Regulatory Review Period (Rule 775(c))

1. Period Pursuant to Paragraph (c)(1)

The period defined at 37 C.F.R. §1.775(c)(1) began on September 20, 1989 (the date the IND became effective) and ended on July 15, 1993 (the date the NDA was filed). The (c)(1) period is thus 1394 days.

2. Period Pursuant to Paragraph (c)(2)

The period defined at 37 C.F.R. §1.775(c)(2) began July 15, 1993 (the date of submission of the NDA submitted pursuant to Section 505(b) of the Act) and ended May 31, 1996 (the commercial marketing and use approval date). The (c)(2) period is thus 1051 days.

The total (c)(1) and (c)(2) time period is thus 2445 days.

B. Term of the Patent as Extended (Rule 775(d))

The term of the patent as extended was then calculated to expire on January 5, 2014, pursuant to 37 C.F.R. §1.775(d).

1. (d)(1) Period (Days Subtracted from Regulatory Review Period)

The regulatory review period upon which the period of extension is calculated by subtracting from the regulatory review period as determined in (c)(1) and (c)(2) of this section the following:

(I) The number of days in the periods of paragraphs (c)(1) and (c)(2) above which were on or before January 5, 1988, the issue date of the original patent.

Since no days in the periods of paragraphs (c)(1) and (c)(2) were on or before January 5, 1988, the number of days to be subtracted from the regulatory review period is zero.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) during which the Applicant did not act with due diligence.

In Applicant's opinion, marketing applicant acted with due diligence as defined at 35 U.S.C. §156(d)(3) during the above calculated periods of paragraphs (c)(1) and (c)(2). Accordingly, zero days are subtracted from the regulatory review period.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(I) and (ii) of this section (ignoring half days).

There are 1394 days in the period defined by paragraph (c)(1). Since there are no reductions in this time period pursuant to paragraphs (d)(1)(I) and (ii) of this section, the number of days remaining in the period defined by paragraph (c)(1) is 1394 days. One-half of 1394 days, ignoring half days for purposes of subtraction, is 697. Subtracting 697 days from 2445 results in a time period of 1748 days.

Thus, the period determined according to paragraph (d)(1) is 1748 days.

2. (d)(2) Date

The number of days determined in paragraph (d)(1), 1748 days, added to the original term of the patent, i.e., 17 years from the original filing date, results in an extended patent expiration date of January 5, 2014.

3. (d)(3) Date

Fourteen years added to the May 31, 1996, date of approval under the Federal Food, Drug and Cosmetic Act, yields an extended patent expiration date of May 31, 2010.

4. (d)(4) Date

Comparing the extended terms determined according to paragraphs (d)(2) and (d)(3), the earlier date is May 31, 2010.

5. (d)(5) Date

The original patent issued after September 24, 1984. Five years added to the original expiration date of the patent is March 24, 2014.

By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(I) of this section with each other, the earlier date is May 31, 2010.

6. (d)(6) Date

The original patent was issued after September 24, 1984. This section thus does not apply.

XIII. ACKNOWLEDGMENT OF DUTY TO DISCLOSE

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. §1.765.

XIV. APPLICATION FEE

Applicant submits herewith a check for $1060.00 in payment of the fee set forth at 37 C.F.R. §1.20(j).

The Commissioner is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to deposit Account No. 02-4800.

XV. CORRESPONDENCE ADDRESS

Please direct all correspondence and inquiries regarding this matter to:

Norman H. Stepno
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404
Phone: (703) 836-6620

XVI. DUPLICATE OF APPLICATION AND CERTIFICATION

Applicant encloses herewith a copy of the present application papers, and certifies that said copy is a duplicate of the application papers. For the convenience of the Senior Legal Advisor of the Patent Office, Applicant is also enclosing three (3) additional copies of the application.

XVII. DECLARATION

A Declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto.

In view of the foregoing, an extension of the term of the above identified patent is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____

Norman H. Stepno
Registration No. 22,716
Donna M. Meuth
Registration No. 36,607

Post Office Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 26, 1996

Patent
Attorney's Docket No. 010095-003d

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of	)	
	)	
Braham Shroot, et al	)	
	)	
U.S. Patent No.: RE 34,440	)	Attn: Box Patent Extension
	)	
Reissued: November 9, 1993	)	Issued as U.S. Patent No. 5,098,895
	)	on March 24, 1992
For: BENZONAPHTHALENE	)	
DERIVATIVES, A PROCESS FOR	)	
THEIR PREPARATION AND THEIR	)	
USE IN THERAPEUTIC AND	)	
COSMETIC COMPOSITIONS	)	

DECLARATION UNDER 37 C.F.R. §1.740(a)(17)

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Donna M. Meuth, do hereby declare as follows:

I am a patent attorney or agent for the owner of record of the above identified U.S. Patent No. Re. 34,440 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, and have general authority from the owner to act on behalf of the owner in patent matters, including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740.

I have reviewed and understand the contents of the application being submitted herewith.

I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710.

I believe that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations.

I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Donna M. Meuth
Registration No. 36,607

Post Office Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 26, 1996

US00RE34440E

United States Patent [19]

Shroot et al.

[11] E Patent Number: Re. 34,440

[45] Reissued Date of Patent: Nov. 9, 1993

[54] **BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS**

[75] Inventors: **Braham Shroot**, Antibes; **Jacques Eustache**, Grasse; **Jean-Michel Bernardon**, Nice, all of France

[73] Assignee: **Centre International de Recherches Dermatologiques (C.I.R.D.)**, Valbonne, France

[21] Appl. No.: **913,897**

[22] Filed: **Jul. 16, 1992**

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 5,098,895
Issued: Mar. 24, 1992
Appl. No.: 502,122
Filed: Mar. 30, 1990

U.S. Applications:

[62] Division of Ser. No. 120,958, Nov. 16, 1987, Pat. No. 4,940,696, which is a division of Ser. No. 850,145, Apr. 10, 1986, Pat. No. 4,717,720.

[30] **Foreign Application Priority Data**

Apr. 11, 1985 [LU] Luxembourg 85849

[51] **Int. Cl.**[5] **A61K 31/435**; A61K 31/19; B01J 29/04; B01J 29/06

[52] **U.S. Cl.** **514/62**; 514/63; 514/237.5; 514/255; 514/319; 514/844; 514/845; 514/859; 514/863; 514/913; 514/914; 514/533; 514/544; 514/559; 514/569; 514/617; 514/618; 514/619; 514/620; 514/621; 514/622; 514/682; 514/700; 514/712; 514/717; 514/718; 514/719; 514/721; 514/730; 514/732

[58] **Field of Search** 514/63, 237.5, 533, 514/544, 569, 718

[56] **References Cited**

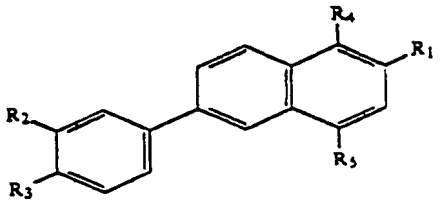
U.S. PATENT DOCUMENTS

4,940,696 7/1990 Shroot et al. 546/14

Primary Examiner—Robert W. Ramsuer
Attorney, Agent, or Firm—Cushman, Darby & Cushman

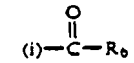
[57] **ABSTRACT**

A benzonaphthalene compound has the formula

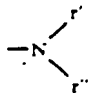


(I)

wherein R_1 represents



or (ii) $—CH_2OH$; R_6 represents



or OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' or r" represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid or a sugar, or together form a heterocycle; R_2 represents hydrogen, alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radial; R_3 represents hydrogen, hydroxy, alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical, a thiocycloaliphatic radical or $—O—Si(CH_3)_2—R_8$ wherein R_8 represents lower alkyl; and R_4 and R_5 represent hydrogen, lower alkyl, hydroxy or lower acyloxy.

This compound is useful in the topical and systemic treatment of dermatologic diseases and in the treatment of the degeneration of conjunctive tissues. The compound also possesses anti-tumor activity.

4 Claims, No Drawings

BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This is a division of application Ser. No. 07/120,958, filed Nov. 16, 1987, now U.S. Pat. No. 4,940,696, which is a division of Ser. No. 06/850,145, filed Apr. 10, 1986, now U.S. Pat. No. 4,717,720.

The present invention relates to benzonaphthalene derivatives, to a process for preparing them and to their use in therapeutic and cosmetic compositions.

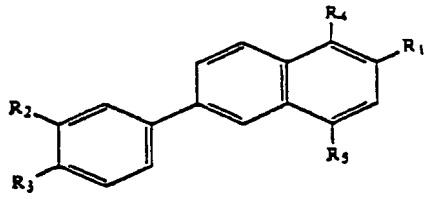
These new benzonaphthalene derivatives are usefully employed in the topical and systemic treatment of dermatological diseases linked to keratinization disorders (differentiation—proliferation) and dermatological diseases, or others, with inflammator and/or immunoallergic components and in the treatment of diseases attributable to the degeneration of conjuctive tissue, The benzonophthalene derivatives of the present invention also exhibit anti-tumor activity. Moreover, these derivatives can be employed in the treatment of atopy be it cutaneous or respiratory.

The benzonaphthalene derivatives of the present invention are also usefully employed in the field of ophthalmology and principally in the treatment of corneopathies.

A number of compounds have already been proposed for the various treatments noted above and principally compounds known under the designation of "retinoids" of which the most well-known ones are the trans and cis retonic acids (tretinoin and isotretinoin) and etretinate.

Compared to these known compounds, the benzonaphthalene derivatives according to the present invention exhibit a strong activity and better stability to light and to oxygen of the air.

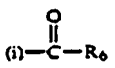
The benzonaphthane derivatives of the present invention can be represented by the following formula:



(I)

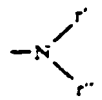
wherein

R_1 represents:



or (ii) $—CH_2OH$,

R_6 represents



or $—OR_7$ represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono- or polyhydroxyalkyl, aryl optionally substituted or a residue of an amino acid or aminated sugar or r' and R'' taken together form a heterocycle.

R_2 represents hydrogen, branched or straight chain alkyl having 1-carbon atoms, alkoxy having 1–4 carbon atoms or a cycoaliphatic group,

R_3 represents hydrogen, hydroxy, straight or branched chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic group substituted or not, a thio-cycloaliphatic group of the formula $—O—Si(CH_3)_2—R_8$ wherein R_8 represents linear or branched lower alkyl.

R_4 and R_5 each independently represent hydrogen, lower alkyl, hydroxy or a lower acyloxy group, and the salts of the said benzonaphthalene derivatives of Formula I.

By the expression "lower alkyl" is meant alkyl radicals having from 1–6 carbon atoms and principally methyl, ethyl, isopropyl, butyl and tert.butyl.

The term "alkoxy" is intended to include radicals having 1–10 carbon atoms and principally methoxy, ethoxy, isopropoxy, hexyloxy and decyloxy radicals.

By the expression "lower acyloxy"is meant radicals having 1–4 carbon atoms and principally acetyloxy and propionyloxy radicals.

By the term "monohydroxyalkyl" is meant a monohydroxy substituted radical having 2 or 3 carbon atoms, principally, 2-hydroxy ethyl and 2- hydroxypropyl.

Representative residues of aminated sugars include those derived from glucosamine, galactosamine and mannosamine.

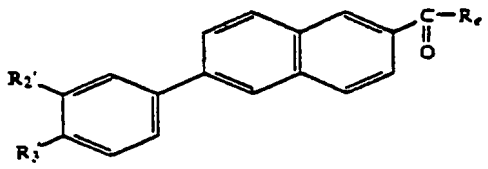
By the terms "polyhydroxyalkyl" is meant an alkyl radical having 3–6 carbon atoms substituted 2–5 hydroxyl groups, such as 2,3-dihydroxy propyl, 1,3-dihydroxy propyl, or the residue of pentaerythritol.

The term "cycloaliphatic" is meant to include a mono or polycyclic radical such as, for example, 1-methyl cyclohexyl or 1-adamantyl.

The preferred thiocycloaliphatic radical is, principally, 1-adamantylthio.

r' and r'' together form a heterocycle, it is preferably a piperidino, piperazino, morphilino or pyrrolidino radical.

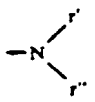
The preferred compounds of Formula I are more particularly those having the following formula:



(II)

wherein

R'_6 represents



or —OR'7,

r' and r'' each independently represent hydrogen or lower alkyl, or r' and r'' taken together form a morpholino radical,

R'7 represents hydrogen or lower alkyl,

R'2 represents hydrogen, alkyl, alkoxy or 1 -adamantyl, and

R'3 represent hydrogen, hydroxy, alkyl, alkoxy or 1 -adamantylthio.

Representative compounds of the present invention include:

(1) 6-(3-methylphenyl)-2-naphthoic acid and its methyl ester.

(2) 6-(4-tert.butyl phenyl)-2 -maphtoic acid and its methyl ester,

(3) 6-(3-tert.butyl phenyl)-2-naphthoic acid and its methyl ester,

(4) 6-(3,4-dimethoxy phenyl)-2-naphthoic acid and its methyl ester,

(5) 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid and its methyl ester,

(6)-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid and its methyl ester,

(7) the methyl ester of 6-[3-(1-adamantyl)-4-tert.butyl dimethylsilyloxyphenyli-2-naphthoic acid,

(8) the methyl ester of 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid,

(9) 6-3-(1-adamantyl-4-hydroxyphenyl]-2-naphthoic acid.

(10) the methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

(11) 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphtoic acid,

(12) the methyl ester of 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(13) 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(14) the methyl ester of 6-3-(1-adamantyl)-4-methoxyphenyl]-4-acetoxy-1-methyl-2-naphthoic acid,

15) 6-3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid,

(16) the methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-4-hydroxy-1-methyl-2-naphthoic acid,

(17) the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid,

(18) 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2 naphthoic acid,

(19) 6-[3-(1-adamanty)-4-methoxyphenyl]-2-naphthalene methanol.

(20) the ethylamide of 6-[3-adamantyl)-4-methoxyphenyl]2-naphthoic acid,

(21) the morpholide of 6-3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,

(22) the methyl ester of 6-[3-tert.butyl-4-methoxyphenyl]-2-naphthoic acid,

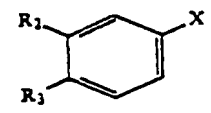
(23) 6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid,

(24) the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid, and

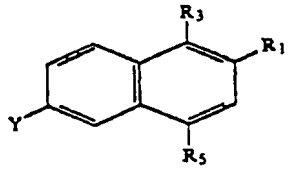
(25) 6-[3-(1,1-dimethyldecyl)-4 -methoxyphenyl]-2-naphthoic acid.

The present invention also relates to a process for preparing the compounds of Formula I.

According to this process the compounds of Formula I are obtained by a coupling reaction between a halogenated compound of Formula III and a halogenated derivative of naphthalene of Formula IV:



(III)



(IV)

wherein

R_1 to R_5 have the same meanings as those given above for Formula I and

X and Y represent Cl, Br, F or I.

According to this coupling reaction, the halogenated compound of Formula III is transformed into its magnesium, lithium or zinc form in accordance with methods described in the literature and is coupled with the halogenated naphthalene derivative of Formula IV by employing, as a reaction catalyst, a transition metal or one of its complexes.

Particularly preferred catalysts are those derived from nickel or palladium and more particularly the compounds of NiII ($NiCl_2$) with various phosphines.

The coupling reaction is generally carried out at a temperature between −20° and +30° C. in an anhydrous solvent such as, for example, dimethylformamide or tetrahydrofuran.

The resulting product can be purified by recrystallization or silica column chromatography.

Obviously, the choice of the halogenated naphthalene derivative of Formula IV, for use in the coupling reaction with the halogenated compound of Formula III, must be such that it can lead, by subsequent reaction, to the various meanings of the R_1 radical given above.

When the compounds according to the present invention are provided in salt form, it is a question of salts of an alkali or alkaline earth metal or of an organic amine when the compounds have at least one free acid function.

The present invention also relates to a medicinal composition comprising as the active principle thereof the compounds of Formula I as defined above.

These compounds exhibit excellent activity in the test for inhibiting ornithine decarboxylase after induction, by "tape stripping" the body of a nude rat. This test is considered a measure of the activity of the retinoids with regard to cellular proliferation phenomenon.

For instance, it has been noted that in this test, 6-[3(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid exhibits an effective dose between 5 and 22 nmoles applied per cm^2.

The compounds according to the invention also exhibit a strong activity in the differentiation test of embryonic tetracarcinoma F9 rat cells (Cancer Research 43, page 5268, 1983).

As an illustration, 6-[3-(1-adamantyl)-4-methoxyphenyl]2-naphthoic acid, at a 0.01 micromolar concentration induces the differentiation of F9 carcinoma cells in endoderm cells. 6-(3-tert.butyl phenyl)-2-naphthoic acid acts in the same fashion at a concentration of 1 micromolar.

Moreover, the irritation test carried out on a rabbit has shown that the compounds of Formula I are less irritating than known retinoids of analogous structure. Moreover, their acute toxicity is weaker.

The compounds of the present invention are indeed particularly suitable for the treatment of dermatological diseases linked to a keratinization disorder (differentiation, proliferation), as well as dermatological diseases or others with inflammatory and/or immunoallergic components such as principally:

acne vulgaris, comedons or polymorphs, solar acne seniles and medicamental or professional acne;

extensive and/or severe forms of psoriasis, and other keratinization disorders, and principally ichtyosis and ichtyosiform states;

Darier disease;

palmo-plantary keratodermy;

leucplasies and leucoplasiform states, lichen plan;

all dermatological proliferations, benign or malignant, severe or extended.

They are also active for certain rheumatic diseases principally psoriasic rheumatism, for cutaneous or respiratory atopies, as well as for certain ophthalmologic disorders relative to the corneopathies.

The present invention also relates to medicinal compositions containing at least one compound of Formula I, as defined above and/or a salt thereof.

The present invention thus relates to a new medicinal composition, intended principally for the treatment of the above-mentioned diseases, comprising in a pharmaceutically acceptable support, at least one compound of Formula I and/or a salt thereof.

As has been indicated previously, the benzonaphthalene derivatives according to the present invention, relative to known retinoids, exhibit better stability against light and oxygen, this being essentially due to the fact that they do not possess any easily isimerized double bonds.

The compounds according to the present invention are generally administered at a daily dosage of about 2 μg/kg to 2 mg/kg of body weight.

As vehicles or supports of these compositions, there can be employed any conventional support, the active compound being found either in the dissolved state or in the dispersed state in the vehicle or support.

The composition can be administered enterally, parenterally, topically or ocularly. When administered enterally, the medicinal composition can be provided in the form of tablets, gelules, lozenges, syrups, suspension, solutions, powders, granules or emulsions. When administered parenterally the medicinal composition can be provided in the form of solutions or suspensions for perfusion or injection.

When administered topically, the pharmaceutical compositions based on the compounds in accordance with the present invention can be provided in the form of ointments, tinctures, creams, pomrades, powders, impregnated pads, buffers, solutions, lotions, gels, sprays or even suspensions.

These compositions for topical application or administration can be provided either under anhydrous form, or in aqueous form according to clinical indications.

When administered ocularly, the compositions are principally eyewashes.

The topical or ocular composition contains preferably between 0.0005 and 5 weight percent of the active compound based on the total weight of the composition.

The compounds of Formula I, according to the present invention also find use in the cosmetic field, in particular in body and hair hygiene and principally for acne, hairgrowth, preventing hair fallout, to combat against the oily appearance of the skin or hair, in the protection against harmful effects of the sun or in the treatment of physiologically dry skin.

The present invention then also envisages a cosmetic composition containing in a cosmetically acceptable support at least one compound of Formula I and/or a salt thereof, this composition being provided principally in the form of a lotion, gel, soap or shampoo.

The concentration of the compound(s) of Formula I in the cosmetic compositions is between 0.0005 and 2 weight percent, preferably between 0.01 and 1 weight percent, based on the total weight of the composition.

The medicinal and cosmetic compositions according to the present invention can contain inert or even pharmacodynamic or cosmetically active ad3uvants and principally: hydrating agents such as thiamorpholinone and its derivatives or urea; antiserbottheic agents such as S-carboxymethylcysteine, S-benzyl cysteamine and their derivatives, or tioxolone; antibiotics such as erythromycin, neomycin or the tetracyclines; agents favoring hair growth such as "Minoxidil" (2,4-diamino-6-piperdinopyrimidine-3-oxide) and its derivatives, Diazoxide and Phenytoin; steroidal anti-inflammatory agents: carotenoids and principally β-carotene; and antipsoriasic agents such as anthralin and its derivatives, 5,8,11,14-eicosatetrainoic acid and 5,8,11-triynoic acid.

The compositions according to the present invention can also contain flavor improving agent, preservatives, stabilizers, humidity regulating agents, pH regulating agents, osmotic pressure modifying agents, emulsifiers, UV-A and UV-B filters and antioxidants such as α-tocopherol, butylhydroxy anisole or butylhydroxy toluene.

The following non-limiting examples illustrate several examples for the preparation of the active compounds of Formula I according to the present invention, as well as examples of compositions containing these active compounds.

EXAMPLE 1

Methyl ester of 6-(3-methylphenyl)-2-naphtholic acid. Compound of Formula II wherein R'_3=H and R'_2=—CH_3 and R'_6=—OCH_3

342 mg (2 mmol) of 3-bromotoluene in 4 ml of THF are converted into the corresponding magnesium form and then treated with an equivalent of zinc chloride to provide the corresponding zinc derivative. There are successfully added 310 mg (1.17 mmol) of methyl 6-bromo-2- naphthoate and 10 mg (0.02 mmol) of $NiCl_2$/1,2-(diphenylphosphino)ethane—DPPE—as the catalyst. The reaction mixture is stirred at ambient temperature for 30 minutes and the mineral salts are then removed by passing the reaction mixture through a 2×3 cm silica column. The reaction mixture is then evaporated to dryness and the residue is chromatographed (HPLC column—Zorbax sil), using as the eluant, a mixture of cyclohexane (75%) and ether (25%). The product thus recovered has an Rf=0.45 (silica

plate, eluant: hexane 50%, dichloromethane 50%) and crystallizes on evaporation of the chromatography solvents. The yield is 84%. Melting point—107° C.

EXAMPLE 2

Methyl ester of 6-(4-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=H. R'_3=—$C(CH_3)_3$ and R'_6=—OCH_3

In a manner analogous to Example 1, starting with 639 mg (3.0 mmol) of 4-bromo tert.butyl benzene and 465 mg (1.75 mmol) of methyl 6-bromo-2-naphthoate, 0.30 g of the expected product is obtained. Yield—54%. Melting point —154° C.

EXAMPLE 3

Methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_3=H. R'_2=—$C(CH_3)_3$ and R'_6=—OCH_3

3.50 g (16.4 mmol) of 3-tert.butyl bromobenzene are added to a suspension of magnesium (0.44 g-18 m Atg) in 20 ml of dry tetrahydrofuran. The reaction is initiated by addition of an iodine crystal and continued at 50° C. for 30 minutes.

2.46 g (18 mmol) of anhydrous zinc chloride dissolved in 20 ml of dry tetrahydrofuran are then added and after 15 minutes, the reaction mixture is cooled to 0° C. At this point, 3.63 g (13.7 mmol) of methyl 6-bromo-2-napthoate and 86 mg (0.26 mmol) of the $NiCl_2$/DPPE complex are added to the reaction mixture.

After stirring for 1 hour at ambient temperature, 100 ml of water are added and the mixture is extracted with ether. After washing the organic phase with a saturated solution of sodium bicarbonate, and water, then drying (sodium sulfate) and evaporating the solvents, the resulting residue is recystallized in heptane, 3.12 g of the methyl ester of 6-(1-tert.butyl phenyl)-2-napthoic acid which melts at 138° C. are obtained.

EXAMPLE 4

6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_3=H. R'_2=—$C(CH_3)_3$ and R'_6=OH

1.0 g (3.14 mmol) of the methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid obtained in Example 3 is added to a mixture of 95% ethanol (40 ml) and soda (4 ml, 5N).

The mixture is heated at 60° C. for 2 hours at which point 50 ml of water are added and the mixture is acidified to pH 1 with 2N HCl. The acidified mixture is then extracted with ether and the organic phase is washed with water until neutral. After drying (sodium sulfate) and evaporation of the solvent, 6-(3-tert.butyl phenyl)-2-naphthoic acid (900 mg) which sublimes at 190° C. is obtained.

EXAMPLE 5

Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_2=H, R'_3=1-adamantylthio and R'_6=—OCH_3 (a) p-(1-adamantylthio) bromobenzene.

3.78 g (20 mmol) of p-bromothiophenol, 3.04 g (20 mmol) of 1-adamantanol and 10 ml of trifluoroacetic acid are stirred at ambient temperature for 8 hours and then poured into water. Sodium bicarbonate is added until the mixture is neutral at which time it is extracted with methylene chloride. The organic phase is dried and evaporated. After recrystallization in isooctane. 5.9 g of the expected product re obtained. Yield—92%. Melting point: 121°–122° C.

(b) Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid 0.64 g (2.65 m Atg) of magnesium suspended in 10 ml of tetrathydrofuran (THF) are treated slowly with 5.7 g (17.6 mmol) of p-(1-adamanthylthio) bromobenzene. After heating at reflux for 2 hours and cooling to 20° C., 2.4 g (17.6 mmol) of anhydrous Zn Cl_2 are added. The mixture is stirred for one hour at 20° C. at which point 2.8 g (10.4 mmol) of methyl 6-bromo-2-naphthoate are added and then 92 mg of $NiCl_2$/1,2-(diphenylphosphino) ethane-DPPE complex are added.

The mixture is stirred at ambient temperature for 2 hours, poured into water, extracted with methylene chloride, washed with sodium bicarbonate, dried and then evaporated. The residue is recrystallized in a mixture of diisopropyl oxide and ethyl acetate. 3.7 g of the expected product are obtained. Yield—84%. Melting point: 189°–190° C.

EXAMPLE 6

6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid Compound of Formula II wherein R'_2=H, R'_6=OH and R'_3=1-adamantylthio

3 g (7mmol) of the ester obtained in Example 5(b) are treated with a solution of soda in methanol (150 ml, 5N). The reaction mixture is heated at reflux for 12 hours, evaporated, taken up in water and acidified with concentrated HCl. The resulting solid is filtered and dried under a vacuo of phosphoric anhydride. The resulting white solid is pulverized in methanol at reflux, cooled and filtered. 2.5 g of the expected product are thus obtained. Yield—86%. Melting point: 334°–336° C.

EXAMPLE 7

Methyl ester of 6-(3,4-dimethoxy phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=R'_3=R'_6=—OCH_3

0.93 g (38.3 mAtg) of magnesium in 20 ml of THF are slowly treated with 5.5 g (25.5 mmol) of 4-bromoveratrole. At the end of the addition, the mixture is heated at reflux for two hours, and then cooled. At this point 3.48 g (25.5 mmol) of anhydrous $ZnCl_2$ are added and the mixture is stirred one hour at ambient temperature. 3.98 g (15 mmol) of methyl 6-bromo-2-naphthoate are then added followed by the addition of 130 mg of $NiCl_2$/DPPE complex. The mixture is stirred for two hours at ambient temperature and then poured into water and extracted with dichloromethane. The organic phase is dried and evaporated. The residue is recyrstallized in a mixture of isopropyl ether and ethyl acetate. 3.4 g of the expected product are obtained. Yield—70%. Melting point: 147°–148° C. EXAMPLE 8

6-(3,4-dimethoxyphenyl-2-naphthoic acid. Compound of Formula II wherein R'_2=R'_3=—OCH_3 and R'_6=OH

2.6 g (8 mmol) of the ester obtained in Example 7 are treated with a solution of soda in methanol (200 ml, 2N). The reaction mixture is heated at reflux for 8 hours, evaporated, taken up in water, acidified with concentrated HCl, and filtered. The solid thus obtained is dried

under a vacuum (on P_2O_5) The resulting white solid is pulverized in methanol at reflux, cooled and then filtered. 2.3 g of the expected product are obtained.

EXAMPLE 9

Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_3—OCH_3, R'_2=1-adamantyl and R'_6=OCH_3

(a) 2-(1-adamantyl)-4-bromophenol

34.6 g (200 mmol) of p-bromophenol and 30.4 g (200 mmol) of 1 -adamantanol are dissolved in 100 ml of dichloromethane. To the resulting solution there are slowly added 10 ml of concentrated sulfuric acid. The mixture is stirred for 8 hours at ambient temperature poured into water, neutralized with sodium bicarbonate, extracted with methylene chloride, dried and evaporated. After recrystallization in isooctane 52.8 g of the expected product are obtained. Yield—86%. Melting point: 140°–141° C.

(b) 2 -(1-adamantyl)-4 -bromoanisole

To a suspension of sodium hydride (80% in oil, 4.32 g, 144 mmol) in 50 ml of THF, there are slowly added, while maintaining the temperature at 20° C., 36.8 g (120 mmol) of 2-(1-adamanyl)-4-bromophenol. The mixture is stirred for 1 hour at ambient temperature at which point 9 ml (144 mmol) of methyl iodide are added. The mixture is then stirred for 2 hours at 20° C., poured into water, extracted with ether, dried and evaporated. The product is purified by passage through a silica column (10×30 cm), eluting with a mixture of hexane (90%) and dichloromethane (10%). On evaporation, 26.2 g of a white solid are obtained. Yield—68%. Melting point: 138°–139° C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl-9 -2-naphthoic acid

To a suspension of magnesium (1.64 g, 67.5 m Atg) in 30 ml of THF, there is added a solution of 1.4 g (4.5 mmol) of 2-(1-adamantyl)-4-bromoanisole and 0.39 ml of dibromoethane of 10 ml of THF. The mixture is stirred until the reaction is initiated and then there is slowly added a solution of 13.3 g (40.8 mmol) of 2-(1-adamantyl)4-bromoanisole in 90 ml of THF. The mixture is heated at reflux for 2 hours, and then cooled to 20° C. There are then added 6.2 g (45 mmol) of anhydrous $ZnCl_2$. The mixture is stirred for 1 hour at 20° C. at which point 7.95 g (30 mmol) of methyl 6-bromo-2-naphthoate are added followed by the addition of 300 g of $NiCl_2$/DPPE complex. The mixture is stirred again for 2 hours at 20° C., poured into water, extracted with CH_2Cl_2, dried and evaporated. The product is isolated by column chromatography, eluting with a mixture of heptane (70%) and dichloromethane (30%) and then recrystallized in ethyl acetate. 12.2 g of the expected product are obtained. Yield—78%. Melting point: 222°–223° C.

EXAMPLE 10

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'=OCH_3, R'_2=1-adamantyl and R'_6=OH.

10.5 g of the ester obtained in Example 9(c) are treated with a solution of soda in methanol (200 ml, 4.2N). The mixture is heated at reflux for 48 hours. The solvents are evaporated and the resulting residue is taken up in water and acidified with concentrated HCl.

The solid is filtered and dried under a vacuum over phosphoric anhydride.

The resulting white solid is recrystallized in a mixture of THF and the ethylacetate. 8.2 g of the expected product are obtained. Yield—81%. Melting point: 325°–327° C.

EXAMPLE 11

Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyl dimethylsilyloxylphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=2-adamantyl, R_3=$OSi(CH_3)_2C_3H_7$ and

$$R_1 = -\overset{O}{\overset{\|}{C}}OCH_3$$

(a)

2-(adamantyl)-4-bromo-1-tert.butyldimethylsilyloxybenzene 30.7 g of 2- adamantyl-4-bromophenol (100 mmol) are dissolved in DMF (200 ml). There are then added triethylamine (15.4 ml, 110 mmol) and 4-N,N-dimethylaminopyridine (DMAP, 500 mg, 4 mmol).

To the resulting solution there is slowly added a solution of tert.butyldimethylsilyl chloride (15.7 g, 104 mmol) in DMF (100 ml). The mixture is stirred at ambient temperature for 4 hours, poured into water, extracted with ether, dried ($MgSO_4$) and evaporated. The residue is dissolved in hexane and purified by passage through a silica column (eluant: hexane). 36.2 g (86%) of 2-adamantyl-4-bromo-1-tert.butyldimethylsilyloxybenzene are obtained. Melting print. 111° C.

(b) Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyldimethyl siloxyphenyl]-2-naphthoic acid 33.3 g (79 mmol) of the compound produced in part (a) above, dissolved in 200 ml of THF are slowly added to a suspension of magnesium (2.9 g 118 Atg) in 60 ml of THF. Once the addition is complete, the mixture is heated at reflux for 2 hours at which point the temperature of the mixture is permitted to return to ambient temperature. 10.8 g (79 mmol) of anydrous zinc chloride are added and the mixture is stirred for one hour at ambient temperature, at which point 10.5 g (39.5 mmol) of methyl 6-bromo-2-naphthoate and 500 g of $NiCl_2$/DPPE complex are added. This mixture is then stirred for 2 hours at ambient temperature, poured into water, extracted with CH_2Cl_2, dried and evaporated. The residue is chromatographed on a silica column (eluant: mixture of heptane (70%) and ether (30%). 18.5 (90%) of the methyl ester of 6-3-(1-adamantyl)-4-tert.butyldimethylsilyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 152°–153° C.

EXAMPLE 12

Methyl ester of 6[3-(1-adamantyl)-4-hydroxyphenyl 2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OH and R_1=$COOCH_3$

17.5 g (33 mmol) of the ester produced in Example 11 are dissolved in 300 ml of THF. To this solution there is added 36.6 ml of a molar solution of tetrabutylam-

monium flouoride in THF. The mixture is stirred for 2 hours at ambient temperature, poured into water and extracted with CH_2Cl_2. The organic phase is recovered, dried ($MgSo_4$), and the solvents evaporated. The resulting residue is recrystallized in a mixture of ethylacetate (70%) and THF (30%) to give the expected ester. 11 g (81%). Melting point; 266° C.

EXAMPLE 13

6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OH and R_1=COOH.

5 g (12 mmol) of the ester obtained in Example 12 are treated with 200 ml of methanolic soda (2N), under nitrogen, for 8 hours. The solvents are evaporated and the residue taken up in water and acidified to pH 1 (concentrated HCl). The reaction mixture is filtered, washed with water, the solid product is extracted with ethyl ether, dried ($MgSO_4$) and evaporated. The residue is recrystallized in isoproplether, yielding 3.8 g (79%) of the expected acid. Melting point: 270°–271° C.

EXAMPLE 14

Methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—$OC_{10}H_{21}$ and R_1=$COOCH_3$

(a) 2-(1-adamantyl)-4-bromo-1-decyloxy benzene

To a suspension of sodium hydride (80% in oil, 3.2 g, 104 mmol) in 100 ml of THF, there is slowly added a solution of 2-(1-adamantyl)-4-bromophenol (29 g, 95 mmol) in 200 ml of THF. The mixture is stirred until the evolution of gas ceases at which point 27.8 g (23 ml, 104 mmol) of 1-iododecane and 100 ml of DMF are added. The mixture it stirred for 12 hours at ambient temperature, poured into water, extracted with ether, dried and the solvents evaporated. The resulting residue is purified by passage through a silica column (eluant: heptane), yielding 40.7 g (96%) of 2(1-adamantyl)-4-bromo-1-decyloxybenzene. Melting point: 69°–70° C.

(b) Methyl ester of 6-3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid

In a manner analogous to Example 9c, starting with 17.9 g (40 mmol) of the brominated derivative obtained in part (a) above, and 5.3 g of methyl 6-bromo-2-naphthoate. 7.4 g (67%) of the expected ester are obtained. Melting point: 113°–114° C.

EXAMPLE 15

6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—$OC_{10}H_{21}$ and R_1=COOH

6.3 g (11 mmol) of the ester obtained in Example 14 dissolved in 200 ml of THF are treated at reflux with 200 ml or 2M methanolic soda for 4 hours. The solvents are evaporated and the residue is taken up in water, acidified to Ph 1 (concentrated HCl), filtered, washed with water and the solid is extracted with ether. The extract is dried and the solvent evaporated. The resulting residue is treated with 700 ml of ethyl acetate at reflux. On cooling 5.9 g (97%) of the expected acid are obtained. Melting point: 214°–215° C.

EXAMPLE 16

Methyl ester of 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—OC_6H_{13} and R_1=—$COOCH_3$

5.3 g (13 mmol) of the ester obtained in Example 12 are dissolved in 100 ml of DMF and added to a suspension of NaH (80% in oil; 0.46 g; 15.4 mmol) in DMF (50 ml). The mixture is stirred at ambient temperature until the evolution of gas ceases, as which point 1-iodohexane (3.26 g; 2.3 ml; 15.4 mmol) is added. This mixture is then stirred for 4 hours at ambient temperature, poured into water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column (eluant: mixture of dichloromethane—50% and hexane—50%), then recrystallized in isooctane to give 5.5 g (87%) of the expected pure product. Melting point: 129°–130° C.

EXAMPLE 17

6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—OC_6H_{13} and R_1=—COOH

In a manner analogous to Example 15, starting with 4.2 g (8.4 mmol) of the ester obtained in Example 16, 3.8 g (95%) of 6-[(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 260°–261° C.

EXAMPLE 18

Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-4-acetoxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=—$OCOCH_3$, R_2=1-adamantyl, R_3=—OCH_3 and R_1=—$COOCH_3$

47.6 g (148 mmol) of 2-(1-adamantyl)-4-bromoanisole and 13.9 g (6.3 ml, 74 mmol) of dibromoethane dissolved in 100 ml of THF are added slowly to a suspension of magnesium (5.4 g, 222 mmol) in the THF (1000 ml). The mixture is brought to a reflux for 2 hours at which point zinc chloride (20.2 g. 148 mmol) is added. The mixture is stirred for 1 hour and there are successively added 2.9 g (74 mmol) of methyl 4-acetoxy-6-bromo-1-methyl-2-naphthoate and 500 mg of $NiCl_2$/DPPE complex. This mixture is stirred for 8 hours at ambient temperature, poured into a saturated aqueous solution of ammonium chloride, extracted with CH_2Cl_2, dried and the solvents evaporated. The resulting residue is purified by passage through a silica column (eluant: mixture of hexane, 40%, and CH_2Cl_2, 60%). The resulting product is crystallized in isopropyl ether, yielding 23.5 g (64%) of the expected ester. Melting point: 201°–202° C.

EXAMPLE 19

6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=OH, R_2=1-adamantyl, R_3=OCH_3 and R_1=COOH

23 g (46 mmol) of the ester obtained in Example 18 are treated at reflux for 12 hours with 300 ml of methanolic soda (2N). The solvents are evaporated and the residue is taken up in water and acidified to pH 1 (concentrated HCl1). The solid is filtered, washed with water, dissolved in ethyl ether, dried ($MgSO_4$) and

evaporated The resulting residue is recrystallized in ethyl acetate to give 18.7 g (92%) of the expected acid. Melting point: 281°–283° C.

EXAMPLE 20

Methyl ester of 6-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid Compound of Formula I wherein R_4=CH_3, R_5=OH, R_2=1-adamantyl, R_3=OCH_3 and R_1=$COOCH_3$

17 g (38 mmol) of the acid obtained in Example 19 are treated for 12 hours at reflux with 200 ml of methanol containing 2 ml of sulfuric acid. The solvents are evaporated and the residue is taken up in water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column using as the eluant a 90:10 mixture of ether/THF. The product is recrystallized in ethyl acetate to obtain the expected pure ester—15 g (86%). Melting point: 272°–274° C.

EXAMPLE 21

Methyl ester of 6[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1 =—$COOCH_3$ (a) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethylaminothiocarbonyloxy-1-methyl-2-naphthoate

4.56 g of the ester obtained in Example 20, dissolved in THF (100 ml) are slowly added to a suspension of sodium hydride (80% in oil, 360 mg, 12 mmol) in DMF (50 ml). The mixture is stirred for 1 hour at ambient temperature and then for 1 hour at 40° C. There are then added 1.75 g (14 mmol) of dimethylthiocarbamoyl chloride, and the mixture is stirred initially at ambient temperature for 2 hours and then at 40° C. for 2 hours. The reaction mixture is poured into water, extracted with ether,. dried, and the solvents evaporated. The product is purified by passage through a silica column (eluant: CH_2Cl_2), yielding 4 g (74%) of the expected intermediate product. Melting point: 137°–138° C.

(b) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethyl-carbonythio-1-methyl-2-naphthoate

3.8 g (7 mmol) of the ester obtained above in part (a) are heated under nitrogen at 260° C. for 0.5 hour. The residue is taken up in methylene chloride and purified by passage through a silica column (eluant: CH_2Cl_2). The resulting gum is taken up in isopropyl ether, yielding 3.3 g (87%) of the desired intermediate. Melting point: 201°–202°C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid

The intermediate obtained above in part (b)—(11 g, 20 mmol) is dissolved in 500 ml of ethanol. 20 g of Raney nickel are added and the reaction mixture is heated at reflux for 4 hours. 20 g of nickel are then added and the mixture is heated again for 1 hour, at which point the mixture is cooled, concentrated and taken up in CH_2Cl_2(1000 ml). The precipitate is filtered and the filtrate is recovered, dried and evaporated. The product is purified by passage through a silica column (eluant: CH_2Cl_2) and recrystallized in a mixture of ethyl acetate (90%) and THF (10%), yielding 8 g (90%) of the methyl ester of 6-[3-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Melting point: 238°–239° C.

EXAMPLE 22

6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=H,R_2=1-adamantyl, R_3=OCH_3 and R_1=COOH.

6.8 g (15.4 mmol) of the ester obtained in Example 21(c) are treated as in Example 10 to give 5.8 g (88%) of the corresponding acid. Melting point: 300°–302° C.

EXAMPLE 23

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-napthalene methanol. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1=CH_{20} H

1.3 g (3 mmol) of the ester obtained in Example 9 dissolved in THF (5 ml) are treated with 171 mg (4.5 mmol) of $LiAlH_4$. The mixture is heated at reflux, cooled and treated with a saturated aqueous solution of the double tartrate of sodium and potassium. The reaction mixture is filtered, evaporated to dryness, and the residue is recrystallized in cyclohexane, yielding 1.0 g (83%) of the 6-13-(1-adamantyl)-4-methoxyphenyl]-2-naphthalene methanol. Melting point: 163°–164° C.

EXAMPLE 24

6-[3-(1-adamantyl)-4-methoxyphenyl-9 -2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1=—$CONHC_2H_5$ (a) 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid chloride

4.75 g (1.15 mmol) of the acid obtained in Example 10 in 200 ml of dichloromethane are treated with 2.08 g (2.3 ml, 1.15 mmol) of dicyclohexamine. The mixture is stirred at ambient temperature until dissolution. The solvents are evaporated and the residue taken up in either. The solid thus formed is filtered (6.8 g) and then taken up in methylene chloride (50 ml). 1.37 g (0.85 ml, 1.15 mmol) of thionyl chloride are added. The salt formed is filtered and the filtrate is recovered, evaporated and dried. The resulting solid (3.9 g) is used as such in the following step.

(b) Ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

1.3 g (3 mmol) of the acid chloride produced in (a) above are dissolved in 20 ml of THF. 405 mg (600 µl, 9 mmol) of ethylamine are added and the mixture is stirred for 2 hours at ambient temperature. The mixture is then poured into water, extracted with CH_2Cl_2, dried and evaporated. The residue is recrystallized in ethyl acetate, yielding 1.1 g (85%) of the expected ethylamide. Melting point: 220°–221° C.

EXAMPLE 25

Morpholide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

In a manner analogous to Example 24, starting with 1.3 g of acid chloride produced in part (a) of Example 24 and 780 mg (780 ml, 9 mmol) of morphine, there are obtained 1.3 g (91%) of the expected morpholide. Melting point: 212°–213° C.

EXAMPLE 26

Methyl ester of 6-3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_2=tert.butyl, R'_3=R'_6=OCH_3 (a) 4-bromo-2-tert.butyl anisole

3.10 g (22.6 mmol) of aluminum chloride are added all at once to a mixture of 63.5 g (339 mmol) of p-bromoanisole and 31.4 g (330 mmol) of tert.butyl chloride. The mixture is stirred at ambient temperature until the evolution of gas ceases (about 15 minutes). The mixture is then heated at 80° C. for 15 minutes and poured into ice. 300 ml of water are added and the mixture is extracted with ether.

The organic phase is dried ($MgSO_4$), the solvents evaporated and the residue purified by chromatography on a silica column (eluant: mixture of methylene chloride—10% and hexane—90%). After evaporation of the solvents, 4-bromo-2-tert.butyl anisole under the form of a colorless oil which crystallized on cooling is obtained, 31.9 g (39%).

(b) Methyl ester of 6-3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid

There is slowly added, drop by drop, a solution of 18.8 g (77 mmol) of 4-bromo-2-tert.butyl anisole of 2.26 g (93 mmol) of magnesium turnings and a crystal of iodine. The mixture is heated until the Grignard begins to form, at which point the remainder of the solution containing the brominated derivative is poured in a manner to maintain a regular reflux. Once the addition is complete, the mixture is heated at 40° C. for 30minutes, diluted with 200 ml of THF and cooled to ambient temperature. 12.7 g (93 mmol) of dry zinc chloride in solution in 20 ml of THF are added and the mixture is stirred for 30 minutes at ambient temperature. There are then successively added 12.1 g (46 mmol) of methyl 6-bromo-2-naphthoate and 300 mg of $NiCl_2$/DPPE complex.

The mixture is stirred for 10 hours at ambient temperature. 300 ml of water are added and the THF is evaporated. The remainder is extracted with methylene chloride. The organic phase is dried ($MgSO_4$), filtered, evaporated and purified by passage through a silica column (eluant: mixture of 50% dichloromethane and 50% hexane). After evaporation of the solvents, the resulting residue is recrystallized in hexane to give the expected ester: 11.5 g (72%). Melting point-160° C.

EXAMPLE 27

6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=tert.butyl, R'_3=OCH_3 and R'_6=OH.

In a manner analogous to Example 15, starting with 7.0 g (20 mmol of the ester obtained in Example 26, 6.0 g (90%)of the expected acid are obtained. Melting point: 268° C.

EXAMPLE 28

Methyl ester of 6[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=$C(CH_3)_2C_9H_{19}$, R_3=OCH_3 and R_1=—$COOCH_3$

A solution of 16 g (45 mmol) of 2- (1,1-dimethyldecyl)-4-bromo anisole in 60 ml of THF is slowly added to 1.3 g (54 mmol) of magnesium and a crystal of iodine. The mixture is slightly heated at the beginning of the addition until the reaction of formation of the Grignard is initiated. Then the remainder of the solution containing the brominated derivative is added in a manner to maintain a regular reflux. Once the addition is complete, the mixture is stirred for 30 minutes at 50° C. and then cooled to ambient temperature. 7.4 g (54 mmol) of zinc chloride in solution in 50 ml of THF are added. The mixture is stirred for 30 minutes at ambient temperature, 6.6 g (25 mmol) of methyl 6-bromo-2-naphthoate are added and then 175 mg of $NiCl_2$/DPPE complex. The mixture is stirred for 3 hours at ambient temperature at which point 250 ml of water are added. The THF is eva-porated under reduced pressure and the residue is extracted with dichloromethane, dried and the solvent evaporated. The residue is purified by passage through a silica column (eluant: mixture of 60% dichlorlmethane and 40% hexane). On evaporation, a solid is obtained which is recrystallized twice in hexane to give the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid: 705 g (61%). Melting point: 92° C.

EXAMPLE 29

6-[3-)1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=$C(CH_3)_2C_9H_{19}$, R_3=OCH_3 and R_1=COOH.

In a manner anologous to Example 15, starting with 3.6 g of the ester obtained in Example 28, 3 (87%) of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid are obtained. Melting point: 180° C.

Examples of Compositions

Example A Fatty Cream wherein the active principle is in suspension

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid	0.001 g
A combination of nonionic E/H emulsifiers and a fatty body of mineral origin sold by Goldschmidt under the trade name "Protegin X"	25.00 g
Petrolatum oil	10.00 g
Preservative, sufficient amount	
Water, sufficient amount for	100.00 g

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxy phenyl]-1-methyl 2-2naphthoic acid.

Example B

Skin cream—A fluid cream wherein the active principle is in suspension

Methyl ester of 6-(4-tert-butyl phenyl)-2-naphthoic acid	0.02 g
Sorbitan stearate polyoxyethylenated with 20 moles of ethylene oxide sold by Atlas under the trade name "Tween 60"	5.00 g
Sorbitan monostearate sold by Atlas under the trade name "Span 60"	2.00 g
Cetyl alcohol	5.00 g
Triglycerides of capric and caprylic acids sold by Dynamit Nobel under the trade name "Miglyol 812"	10.00 g
Preservatives, sufficient amount	
Water, sufficient amount for	100.00 g

Example C

Gel for the skin or scalp wherein the active principle is in suspension

Methyl ester of 6-(4-t-butyl phenyl)-2-naphthoic acid	0.10 g
Ethanol	20.00 g
Hydroxypropyl cellulose, sold by Hercules under the trade name "Klucel HF"	2.00 g
Preservative, sufficient amount	
Water, sufficient amount for	100.00 g

Example D

Lotion for the skin

6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid	0.3 g
Polyethylene glycol 400	70.0 g
Ethanol	29.9 g

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Example E

Unguent for the skin

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid	0.001 g
Lanolin	50 g
Vaseline, sufficient amount for	100 g

Example F

Oral composition—0.30 g gelule

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid	0.003 g
Cornstarch	0.060 g
Lactose, sufficient amount for	0.300 g

The resulting powder is packaged in a gelule whose wall is made of gelatin, TiO_2 and a preservative.

Example G

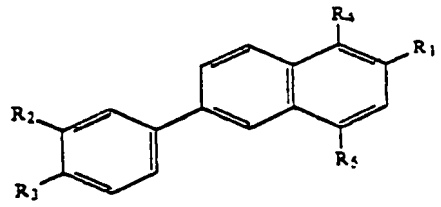
Capsule containing 0.400 g of the following suspension

Ethylamide of 6-[3-(1-adamantyl)-4-methoxy-phenyl]-2-naphthoic acid	0.005 g
Glycerine	0.200 g
Sucrose	0.050 g
Polyethylene glycol 400	0.050 g
Purified water, sufficient amount for	0.400 g

This suspension is packaged in a capsule made of gelatin, glycerine titanium dioxide and water.

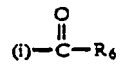
What is claimed is:

1. A process for the treatment of a dermatologic, rheumatismal, respiratory or ophtalmologic disease comprising administering to a person suffering from said disease an effective amount of a composition containing, in a pharmaceutically acceptable vehicle, as the active ingredient thereof a benzonaphthalene compound of the formula



wherein

R_1 represents



or (ii)—CH_2OH,

R_6 represents

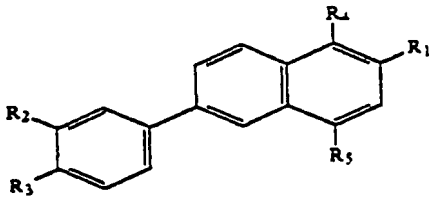
or OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

R_2 represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical,

R_3 represents hydrogen, hydroxy, branched or straight chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical selected from the group consisting of 1-methylcyclohexyl and 1-adamantyl, a thiocycloaliphatic radical, or —O—$Si(CH_3)_2$—R_8 wherein R_8 represents linear or branched alkyl,

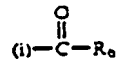
R_4 and R_5 each independently represent hydrogen, lower alkyl, *hydroxy* or lower acyloxy, or salt thereof.

2. A cosmetic composition for both and hair hygiene comprising a cosmetically acceptable vehicle and an effective amount of as the active ingredient at least one benzonaphthalene compound of the formula



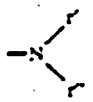
wherein

R_1 represents



or (ii) —CH_2OH.

R_6 represents



OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

R_2 represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical.

R_3 represents hydrogen, hydroxy, branched or straight chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical selected from the group consisting of 1-methylcyclohexyl and 1- adamantyl, a thiocycloaliphatic radical, or —O—$Si(CH_3)_2$—R_8 wherein R_8 represents linear or branches alkyl,

R_4 and R_5 each independently represent hydrogen, lower alkyl, *hydroxy* or lower acyloxy, or a salt thereof.

3. The cosmetic composition of claim 2 wherein said active ingredient is present in an amount ranging from 0.0005 to 2 weight percent based on the total weight of said composition.

4. The cosmetic composition of claim 2 wherein said active ingredient is present in an amount ranging from 0.01 to 1 weight percent based on the total weight of said composition.

* * * * *

US005098895A

United States Patent [19]

Shroot et al.

[11] Patent Number: 5,098,895

[45] Date of Patent: Mar. 24, 1992

[54] **BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS**

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[21] Appl. No.: **502,122**

[22] Filed: **Mar. 30, 1990**

Related U.S. Application Data

[62] Division of Ser. No. 120,958, Nov. 16, 1987, Pat. No. 4,940,696, which is a division of Ser. No. 850,145, Apr. 10, 1986, Pat. No. 4,717,720.

[30] **Foreign Application Priority Data**

Apr. 11, 1985 [LU] Luxembourg 85849

[51] **Int. Cl.**[5] **A61K 31/435**; B01J 29/04; B01J 29/06

[52] **U.S. Cl.** **514/62**; 514/63; 514/237.5; 514/255; 514/319; 514/844; 514/845; 514/859; 514/863; 514/913; 514/914; 514/533; 514/544; 514/559; 514/569; 514/617; 514/618; 514/619; 514/620; 514/621; 514/622; 514/682; 514/700; 514/712; 514/717; 514/718; 514/719; 514/721; 514/730

[58] **Field of Search** 514/844, 845, 859, 863, 514/913, 914, 255, 319, 237.5, 423, 63, 62, 617, 618, 619, 620, 621, 622, 682, 700, 712, 717, 718, 719, 721, 730, 732, 569, 533, 544, 559

[56] **References Cited**

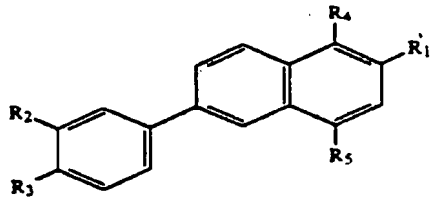
U.S. PATENT DOCUMENTS

4,940,696 7/1990 Shroot et al. 546/14

Primary Examiner—Johann Richter
Attorney, Agent, or Firm—Cushman, Darby & Cushman

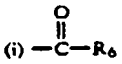
[57] **ABSTRACT**

A benzonaphthalene compound has the formula



(I)

wherein R_1 represents



or (ii) $—CH_2OH$; R_6 represents

or OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' or r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid or a sugar, or together form a heterocycle; R_2 represents hydrogen, alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radial; R_3 represents hydrogen, hydroxy, alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical, a thiocycloaliphatic radical or $—O—Si(CH_3)_2—R_8$ wherein R_8 represents lower alkyl; and R_4 and R_5 represent hydrogen, lower alkyl, hydroxy or lower acyloxy.

This compound is useful in the topical and systemic treatment of dermatologic diseases and in the treatment of the degeneration of conjunctive tissues. The compound also possesses anti-tumor activity.

4 Claims, No Drawings

BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS

This is a division of application Ser. No. 07/120,958, filed Nov. 16, 1987, now U.S. Pat. No. 4,940,696, which is a division of Ser. No. 06/850,145, filed Apr. 10, 1986, now U.S. Pat. No. 4,717,720.

The present invention relates to benzonaphthalene derivatives, to a process for preparing them and to their use in therapeutic and cosmetic compositions.

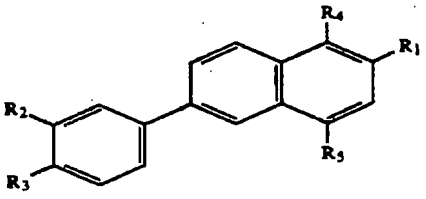
These new benzonaphthalene derivatives are usefully employed in the topical and systemic treatment of dermatological diseases linked to keratinization disorders (differentiation—proliferation) and dermatological diseases, or others, with inflammator and/or immunoallergic components and in the treatment of diseases attributable to the degeneration of conjuctive tissue. The benzonaphthalene derivatives of the present invention also exhibit anti-tumor activity. Moreover, these derivatives can be employed in the treatment of atopy be it cutaneous or respiratory.

The benzonaphthalene derivatives of the present invention are also usefully employed in the field of ophthalmology and principally in the treatment of corneopathies.

A number of compounds have already been proposed for the various treatments noted above and principally compounds known under the designation of "retinoids" of which the most well-known ones are the trans and cis retinoic acids (tretinoin and isotretinoin) and etretinate.

Compared to these known compounds, the benzonaphthalene derivatives according to the present invention exhibit a strong activity and better stability to light and to oxygen of the air.

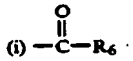
The benzonaphthane derivatives of the present invention can be represented by the following formula:



(I)

wherein

R_1 represents:



or (ii) $—CH_2OH$,

R_6 represents

or $—OR_7$ wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono- or polyhydroxyalkyl, aryl optionally substituted or a residue of an amino acid or aminated sugar or r' and r'' taken together form a heterocycle,

R_2 represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic group,

R_3 represents hydrogen, hydroxy, straight or branched chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic group substituted or not, a thio-cycloaliphatic group of the formula $—O—Si(CH_3)_2—R_8$ wherein R_8 represents linear or branched lower alkyl,

R_4 and R_5 each independently represent hydrogen, lower alkyl, hydroxy or a lower acyloxy group, and the salts of the said benzonaphthalene derivatives of Formula I.

By the expression "lower alkyl" is meant alkyl radicals having from 1–6 carbon atoms and principally methyl, ethyl, isopropyl, butyl and tert.butyl.

The term "alkoxy" is intended to include radicals having 1–10 carbon atoms and principally methoxy, ethoxy, isopropoxy, hexyloxy and decyloxy radicals.

By the expression "lower acyloxy" is meant radicals having 1–4 carbon atoms and principally acetyloxy and propionyloxy radicals.

By the term "monohydroxyalkyl" is meant a monohydroxy substituted radical having 2 or 3 carbon atoms, principally, 2-hydroxy ethyl and 2-hydroxypropyl.

Representative residues of aminated sugars include those derived from glucosamine, galactosamine and mannosamine.

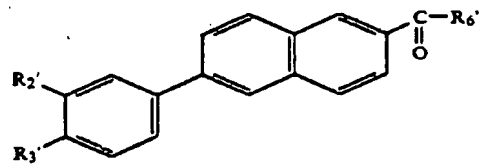
By the term "polyhydroxyalkyl" is meant an alkyl radical having 3–6 carbon atoms substituted 2–5 hydroxyl groups, such as 2,3-dihydroxy propyl, 1,3-dihydroxy propyl, or the residue of pentaerythritol.

The term "cycloaliphatic" is meant to include a mono or polycyclic radical such as, for example, 1-methyl cyclohexyl or 1-adamantyl.

The preferred thiocycloaliphatic radical is, principally, 1-adamantylthio.

r' and r'' together form a heterocycle, it is preferably a piperidino, piperazino, morpholino or pyrrolidino radical.

The preferred compounds of Formula I are more particularly those having the following formula:



(II)

wherein

R'_6 represents

or $—OR'_7$,

r' and r'' each independently represent hydrogen or lower alkyl, or r' and r'' taken together form a morpholino radical,

R'_7 represents hydrogen or lower alkyl,

R'_2 represents hydrogen, alkyl, alkoxy or 1-adamantyl, and

R'_3 represents hydrogen, hydroxy, alkyl, alkoxy or 1-adamantylthio.

Representative compounds of the present invention include:

(1) 6-(3-methylphenyl)-2-naphthoic acid and its methyl ester,

(2) 6-(4-tert.butyl phenyl)-2-naphthoic acid and its methyl ester,

(3) 6-(3-tert.butyl phenyl)-2-naphthoic acid and its methyl ester,

(4) 6-(3,4-dimethoxy phenyl)-2-naphthoic acid and its methyl ester,

(5) 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid and its methyl ester,

(6) 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid and its methyl ester,

(7) the methyl ester of 6-[3-(1-adamantyl)-4-tert.butyl dimethylsilyloxyphenyli-2-naphthoic acid,

(8) the methyl ester of 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid, (9) 6-3-(1-adamantyl-4-hydroxyphenyl]-2-naphthoic acid,

(10) the methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

(11) 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

(12) the methyl ester of 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(13) 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(14) the methyl ester of 6-3-(1-adamantyl)-4-methoxyphenyl]-4-acetoxy-1-methyl-2-naphthoic acid,

(15) 6-3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid,

(16) the methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-4-hydroxy-1-methyl-2-naphthoic acid,

(17) the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid,

(18) 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2naphthoic acid,

(19) 6-[3-(1-adamanty)-4-methoxyphenyl]-2-naphthalene methanol,

(20) the ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]2-naphthoic acid,

(21) the morpholide of 6-3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,

(22) the methyl ester of 6-[3-tert.butyl-4-methoxyphenyl]-2-naphthoic acid,

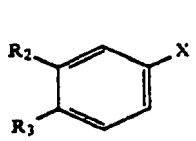
(23) 6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid,

(24) the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid, and

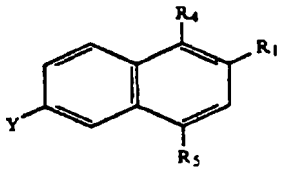
(25) 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid.

The present invention also relates to a process for preparing the compounds of Formula I.

According to this process the compounds of Formula I are obtained by a coupling reaction between a halogenated compound of Formula III and a halogenated derivative of naphthalene of Formula IV:



(III)



(IV)

wherein

R_1 to R_5 have the same meanings as those given above for Formula I and

X and Y represent Cl, Br, F or I.

According to this coupling reaction, the halogenated compound of Formula III is transformed into its magnesium, lithium or zinc form in accordance with methods described in the literature and is coupled with the halogenated naphthalene derivative of Formula IV by employing, as a reaction catalyst, a transition metal or one of its complexes.

Particularly preferred catalysts are those derived from nickel or palladium and more particularly the compounds of NiII ($NiCl_2$) with various phosphines.

The coupling reaction is generally carried out at a temperature between −20° and +30° C. in an anhydrous solvent such as, for example, dimethylformamide or tetrahydrofuran.

The resulting product can be purified by recrystallization or silica column chromatography.

Obviously, the choice of the halogenated naphthalene derivative of Formula IV, for use in the coupling reaction with the halogenated compound of Formula III, must be such that it can lead, by subsequent reaction, to the various meanings of the R_1 radical given above.

When the compounds according to the present invention are provided in salt form, it is a question of salts of an alkali or alkaline earth metal or of an organic amine when the compounds have at least one free acid function.

The present invention also relates to a medicinal composition comprising as the active principle thereof the compounds of Formula I as defined above.

These compounds exhibit excellent activity in the test for inhibiting ornithine decarboxylase after induction, by "tape stripping" the body of a nude rat. This test is considered a measure of the activity of the retinoids with regard to cellular proliferation phenomenon.

For instance, it has been noted that in this test, 6-[3(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid exhibits an effective dose between 5 and 25 nmoles applied per cm^2.

The compounds according to the invention also exhibit a strong activity in the differentiation test of embryonic tetracarcinoma F9 rat cells (Cancer Research 43, page 5268, 1983).

As an illustration, 6-[3-(1-adamantyl)-4-methoxypheny]-2-naphthoic acid, at a 0.01 micromolar concentration induces the differentiation of F9 carcinoma cells in endoderm cells.

6-(3-tert.butyl phenyl)-2-naphthoic acid acts in the same fashion at a concentration of 1 micromolar.

Moreover, the irritation test carried out on a rabbit has shown that the compounds of Formula I are less irritating than known retinoids of analogous structure. Moreover, their acute toxicity is weaker.

The compounds of the present invention are indeed particularly suitable for the treatment of dermatological diseases linked to a keratinization disorder (differentiation, proliferation), as well as dermatological diseases or others with inflammatory and/or immunoallergic components such as principally:

acne vulgaris, comedons or polymorphs, solar acne seniles and medicamental or professional acne;

extensive and/or severe forms of psoriasis, and other keratinization disorders, and principally ichtyosis and ichtyosiform states;

Darier disease;

palmo-plantary keratodermy;

leucoplasies and leucoplasiform states, lichen plan;

all dermatological proliferations, benign or malignant, severe or extended.

They are also active for certain rheumatic diseases principally psoriasic rheumatism, for cutaneous or respiratory atopies, as well as for certain ophthalmologic disorders relative to the corneopathies.

The present invention also relates to medicinal compositions containing at least one compound of Formula I, as defined above and/or a salt thereof.

The present invention thus relates to a new medicinal composition, intended principally for the treatment of the above-mentioned diseases, comprising in a pharmaceutically acceptable support, at least one compound of Formula I and/or a salt thereof.

As has been indicated previously, the benzonaphthalene derivatives according to the present invention, relative to known retinoids, exhibit better stability against light and oxygen, this being essentially due to the fact that they do not possess any easily isomerized double bonds.

The compounds according to the present invention are generally administered at a daily dosage of about 2 μg/kg to 2 mg/kg of body weight.

As vehicles or supports for these compositions, there can be employed any conventional support, the active compound being found either in the dissolved state or in the dispersed state in the vehicle or support.

The composition can be administered enterally, parenterally, topically or ocularly. When administered enterally, the medicinal composition can be provided in the form of tablets, gelules, lozenges, syrups, suspension, solutions, powders, granules or emulsions. When administered parenterally the medicinal composition can be provided in the form of solutions or suspensions for perfusion or injection.

When administered topically, the pharmaceutical compositions based on the compounds in accordance with the present invention can be provided in the form of ointments, tinctures, creams, pomrades, powders, impregnated pads, buffers, solutions, lotions, gels, sprays or even suspensions.

These compositions for topical application or administration can be provided either under anhydrous form, or in aqueous form according to clinical indications. When administered ocularly, the compositions are principally eyewashes.

The topical or ocular composition contains preferably between 0.0005 and 5 weight percent of the active compound based on the total weight of the composition.

The compounds of Formula I, according to the present invention also find use in the cosmetic field, in particular in body and hair hygiene and principally for acne, hairgrowth, preventing hair fallout, to combat against the oily appearance of the skin or hair, in the protection against harmful effects of the sun or in the treatment of physiologically dry skin.

The present invention then also envisages a cosmetic composition containing in a cosmetically acceptable support at least one compound of Formula I and/or a salt thereof, this composition being provided principally in the form of a lotion, gel, soap or shampoo.

The concentration of the compound(s) of Formula I in the cosmetic compositions is between 0.0005 and 2 weight percent, preferably between 0.01 and 1 weight percent, based on the total weight of the composition.

The medicinal and cosmetic compositions according to the present invention can contain inert or even pharmacodynamic or cosmetically active ad3uvants and principally: hydrating agents such as thiamorpholinone and its derivatives or urea; antiseborrheic agents such as S-carboxymethylcysteine, S-benzyl cysteamine and their derivatives, or tioxolone; antibiotics such as erythromycin, neomycin or the tetracyclines; agents favoring hair growth such as "Minoxidil" (2,4-diamino-6-piperidinopyrimidine-3-oxide) and its derivatives, Diazoxide and Phenytoin; steroidal anti-inflammatory agents; carotenoids and principally β-carotene; and antipsoriasic agents such as anthralin and its derivatives, 5,8,11,14-eicosatetrainoic acid and 5,8,11-triynoic acid.

The compositions according to the present invention can also contain flavor improving agents, preservatives, stabilizers, humidity regulating agents, pH regulating agents, osmotic pressure modifying agents, emulsifiers, UV-A and UV-B filters and antioxidants such as α-tocopherol, butylhydroxy anisole or butylhydroxy toluene.

The following non-limiting examples illustrate several examples for the preparation of the active compounds of Formula I according to the present invention, as well as examples of compositions containing these active compounds.

EXAMPLE 1

Methyl ester of 6-(3-methylphenyl)-2-naphthoic acid. Compound of Formula II wherein R'_3=H and R'_2=—CH_3 and R'_6=—OCH_3

342 mg (2 mmol) of 3-bromotoluene in 4 ml of THF are converted into the corresponding magnesium form and then treated with an equivalent of zinc chloride to provide the corresponding zinc derivative. There are successively added 310 mg (1.17 mmol) of methyl 6-bromo-2-naphthoate and 10 mg (0.02 mmol) of $NiCl_2$/1,2-(diphenylphosphino)ethane—DPPE—as the catalyst. The reaction mixture is stirred at ambient temperature for 30 minutes and the mineral salts are then removed by passing the reaction mixture through a 2×3 cm silica column. The reaction mixture is then evaporated to dryness and the residue is chromatographed (HPLC column—Zorbax sil), using as the eluant, a mixture of cyclohexane (75%) and ether (25%). The product thus recovered has an Rf=0.45 (silica plate, eluant: hexane 50%, dichloromethane 50%) and crystallizes on evaporation of the chromatography solvents. The yield is 84%. Melting point—107° C.

EXAMPLE 2

Methyl ester of 6-(4-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=H, R'_3=—$C(CH_3)_3$ and R'_6=—OCH_3

In a manner analogous to Example 1, starting with 639 mg (3.0 mmol) of 4-bromo tert.butyl benzene and 465 mg (1.75 mmol) of methyl 6-bromo-2-naphthoate, 0.30 g of the expected product is obtained. Yield—54%. Melting point—154° C.

EXAMPLE 3

Methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_3=H, R'_2=—$C(CH_3)_3$ and R'_6=—OCH_3

3.50 g (16.4 mmol) of 3-tert.butyl bromobenzene are added to a suspension of magnesium (0.44 g-18 m Atg) in 20 ml of dry tetrahydrofuran. The reaction is initiated by addition of an iodine crystal and continued at 50° C. for 30 minutes.

2.46 g (18 mmol) of anhydrous zinc chloride dissolved in 20 ml of dry tetrahydrofuran are then added and after 15 minutes, the reaction mixture is cooled to 0° C. At this point, 3.63 g (13.7 mmol) of methyl 6-bromo-2-naphthoate and 86 mg (0.26 mmol) of the $NiCl_2$/DPPE complex are added to the reaction mixture.

After stirring for 1 hour at ambient temperature, 100 ml of water are added and the mixture is extracted with ether. After washing the organic phase with a saturated solution of sodium bicarbonate, and water, then drying (sodium sulfate) and evaporating the solvents, the resulting residue is recrystallized in heptane. 3.12 g of the methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid which melts at 138° C. are obtained.

EXAMPLE 4

6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_3=H, R'_2=—$C(CH_3)_3$and R'_6=OH

1.0 g (3.14 mmol) of the methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid obtained in Example 3 is added to a mixture of 95% ethanol (40 ml) and soda (4 ml, 5N).

The mixture is heated at 60° C. for 2 hours at which point 50 ml of water are added and the mixture is acidified to pH 1 with 2N HCl. The acidified mixture is then extracted with ether and the organic phase is washed with water until neutral. After drying (sodium sulfate) and evaporation of the solvent, 6-(3-tert.butyl phenyl)-2-naphthoic acid (900 mg) which sublimes at 190° C. is obtained.

EXAMPLE 5

Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_2=H, R'_3=1-adamantylthio and R'_6=—OCH_3

(a) p-(1-adamantylthio) bromobenzene.

3.78 g (20 mmol) of p-bromothiophenol, 3.04 g (20 mmol) of 1-adamantanol and 10 ml of trifluoroacetic acid are stirred at ambient temperature for 8 hours and then poured into water. Sodium bicarbonate is added until the mixture is neutral at which time it is extracted with methylene chloride. The organic phase is dried and evaporated. After recrystallization in isooctane, 5.9 g of the expected product re obtained. Yield—92%. Melting point: 121°–122° C.

(b) Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid

0.64 g (26.5 m Atg) of magnesium suspended in 10 ml of tetrathydrofuran (THF) are treated slowly with 5.7 g (17.6 mmol) of p-(1-adamantylthio) bromobenzene. After heating at reflux for 2 hours and cooling to 20° C., 2.4 g (17.6 mmol) of anhydrous Zn Cl_2 are added. The mixture is stirred for one hour at 20° C. at which point 2.8 g (10.4 mmol) of methyl 6-bromo-2-naphthoate are added and then 92 mg of $NiCl_2$/1,2-(diphenylphosphino)ethane-DPPE complex are added.

The mixture is stirred at ambient temperature for 2 hours, poured into water, extracted with methylene chloride, washed with sodium bicarbonate, dried and then evaporated. The residue is recrystallized in a mixture of diisopropyl oxide and ethyl acetate. 3.7 g of the expected product are obtained. Yield—84%. Melting point: 189°–190° C.

EXAMPLE 6

6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid Compound of Formula II wherein R'_2=H, R'_6=OH and R'_3=1-adamantylthio

3 g (7 mmol) of the ester obtained in Example 5(b) are treated with a solution of soda in methanol (150 ml, 5N). The reaction mixture is heated at reflux for 12 hours, evaporated, taken up in water and acidified with concentrated HCl. The resulting solid is filtered and dried under a vacuo on phosphoric anhydride. The resulting white solid is pulverized. in methanol at reflux, cooled and filtered. 2.5 g of the expected product are thus obtained. Yield—86%. Melting point: 334°–336° C.

EXAMPLE 7

Methyl ester of 6-(3,4-dimethoxy phenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=R'_3=R'_6=—OCH_3

0.93 g (38.3 mAtg) of magnesium in 20 ml of THF are slowly treated with 5.5 g (25.5 mmol) of 4-bromoveratrole. At the end of the addition, the mixture is heated at reflux for two hours, and then cooled. At this point 3.48 g (25.5 mmol) of anhydrous $ZnCl_2$ are added and the mixture is stirred one hour at ambient temperature. 3.98 g (15 mmol) of methyl 6-bromo-2-naphthoate are then added followed by the addition of 130 mg of $NiCl_2$/DPPE complex. The mixture is stirred for two hours at ambient temperature and then poured into water and extracted with dichloromethane. The organic phase is dried and evaporated. The residue is recrystallized in a mixture of isopropyl ether and ethyl acetate. 3.4 g of the expected product are obtained. Yield—70%. Melting point: 147°–148° C.

EXAMPLE 8

6-(3,4-dimethoxyphenyl-2-naphthoic acid. Compound of Formula II wherein R'_2=R'_3=—OCH_3 and R'_6=OH

2.6 g (8 mmol) of the ester obtained in Example 7 are treated with a solution of soda in methanol (200 ml, 2N). The reaction mixture is heated at reflux for 8 hours, evaporated, taken up in water, acidified with concentrated HCl, and filtered. The solid thus obtained is dried under a vacuum (on P_2O_5) The resulting white solid is

pulverized in methanol at reflux, cooled and then filtered. 2.3 g of the expected product are obtained.

EXAMPLE 9

Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_3—OCH_3, R'_2=1-adamantyl and R'_6=OCH_3

(a) 2-(1-adamantyl)-4-bromophenol

34.6 g (200 mmol) of p-bromophenol and 30.4 g (200 mmol) of 1-adamantanol are dissolved in 100 ml of dichloromethane. To the resulting solution there are slowly added 10 ml of concentrated sulfuric acid. The mixture is stirred for 8 hours at ambient temperature poured into water, neutralized with sodium bicarbonate, extracted with methylene chloride, dried and evaporated. After recrystallization in isooctane 52.8 g of the expected product are obtained. Yield—86%. Melting point: 140°–141° C.

(b) 2-(1-adamantyl)-4-bromoanisole

To a suspension of sodium hydride (80% in oil, 4.32 g, 144 mmol) in 50 ml of THF, there are slowly added, while maintaining the temperature at 20° C., 36.8 g (120 mmol) of 2-(1-adamanyl)-4-bromophenol. The mixture is stirred for 1 hour at ambient temperature at which point 9 ml (144 mmol) of methyl iodide are added. The mixture is then stirred for 2 hours at 20° C., poured into water, extracted with ether, dried and evaporated. The product is purified by passage through a silica column (10×30 cm), eluting with a mixture of hexane (90%) and dichloromethane (10%). On evaporation, 26.2 g of a white solid are obtained. Yield—68%. Melting point: 138°–139° C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid

To a suspension of magnesium (1.64 g, 67.5 m Atg) in 30 ml of THF, there is added a solution of 1.4 g (4.5 mmol) of 2-(1-adamantyl)-4-bromoanisole and 0.39 ml of dibromoethane in 10 ml of THF. The mixture is stirred until the reaction is initiated and then there is slowly added a solution of 13.1 g (40.8 mmol) of 2-(1-adamantyl)-4-bromoanisole in 90 ml of THF. The mixture is heated at reflux for 2 hours, and then cooled to 20° C. There are then added 6.2 g (45 mmol) of anhydrous $ZnCl_2$. The mixture is stirred for 1 hour at 20° C. at which point 7.95 g (30 mmol) of methyl 6-bromo-2-naphthoate are added followed by the addition of 300 g of $NiCl_2$/DPPE complex. The mixture is stirred again for 2 hours at 20° C., poured into water, extracted with CH_2Cl_2, dried and evaporated. The product is isolated by column chromatography, eluting with a mixture of heptane (70%) and dichloromethane (30%) and then recrystallized in ethyl acetate. 12.2 g of the expected product are obtained. Yield—78%. Melting point: 222°–223° C.

EXAMPLE 10

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'=OCH_3, R'_2=1-adamantyl and R'_6=OH.

10.5 g of the ester obtained in Example 9(c) are treated with a solution of soda in methanol (200 ml, 4.2N). The mixture is heated at reflux for 48 hours. The solvents are evaporated and the resulting residue is taken up in water and acidified with concentrated HCl. The solid is filtered and dried under a vacuum over phosphoric anhydride.

The resulting white solid is recrystallized in a mixture of THF and ethyl acetate. 8.2. g of the expected product are obtained. Yield—81%. Melting point: 325°–327° C.

EXAMPLE 11

Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyl dimethylsilyloxylphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=$OSi(CH_3)_2C_3H_7$ and

$$R_1 = -\overset{O}{\overset{\|}{C}}OCH_3$$

(a)

2-(adamantyl)-4-bromo-1-tert.butyldimethylsilyloxybenzene 30.7 g of 2-adamantyl-4-bromophenol (100 mmol)are dissolved in DMF (200 ml). There are then added triethylamine (15.4 ml, 110 mmol) and 4-N,N-dimethylaminopyridine (DMAP, 500 mg, 4 mmol).

To the resulting solution there is slowly added a solution of tert.butyldimethylsilyl chloride (15.7 g, 104 mmol) in DMF (100 ml). The mixture is stirred at ambient temperature for 4 hours, poured into water, extracted with ether, dried ($MgSO_4$) and evaporated. The residue is dissolved in hexane and purified by passage through a silica column (eluant: hexane). 36.2 g (86%) of 2-adamantyl-4-bromo-1-tert.butyldimethylsilyloxybenzene are obtained. Melting print. 111° C.

(b) Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyldimethyl siloxyphenyl]-2-naphthoic acid

33.3 g (79 mmol) of the compound produced in part (a) above, dissolved in 200 ml of THF are slowly added to a suspension of magnesium (2.9 g, 118 Atg) in 60 ml of THF. Once the addition is complete, the mixture is heated at reflux for 2 hours at which point the temperature of the mixture is permitted to return to ambient temperature. 10.8 g (79 mmol) of anhydrous zinc chloride are added and the mixture is stirred for one hour at ambient temperature, at which point 10.5 g (39.5 mmol) of methyl 6-bromo-2-naphthoate and 500 mg of $NiCl_2$/DPPE complex are added. This mixture is then stirred for 2 hours at ambient temperature, poured into water, extracted with CH_2Cl_2, dried and evaporated. The residue is chromatographed on a silica column (eluant: mixture of heptane (70%) and ether (30%). 18.5 (90%) of the methyl ester of 6-3-(1-adamantyl)-4-tert.butyldimethylsilyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 152°–153° C.

EXAMPLE 12

Methyl ester of 6[3-(1-adamantyl)-4-hydroxyphenyl 2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OH and R_1=$COOCH_3$

17.5 g (33 mmol) of the ester produced in Example 11 are dissolved in 300 ml of THF. To this solution there is added 36.6 ml of a molar solution of tetrabutylammonium fluoride in THF. The mixture is stirred for 2 hours at ambient temperature, poured into water and

extracted with CH_2Cl_2. The organic phase is recovered, dried ($MgSo_4$), and the solvents evaporated. The resulting residue is recrystallized in a mixture of ethylacetate (70%) and THF (30%) to give the expected ester. 11 g (81%). Melting point; 266° C.

EXAMPLE 13

6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OH and R_1=COOH.

5 g (12 mmol) of the ester obtained in Example 12 are treated with 200 ml of methanolic soda (2N), under nitrogen, for 8 hours. The solvents are evaporated and the residue taken up in water and acidified to pH 1 (concentrated HCl). The reaction mixture is filtered, washed with water, the solid product is extracted with ethyl ether, dried ($MgSO_4$) and evaporated. The residue is recrystallized in isopropylether, yielding 3.8 g (79%) of the expected acid. Melting point: 270–271° C.

EXAMPLE 14

Methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—$OC_{10}H_{21}$ and R_1=$COOCH_3$

(a) 2-(1-adamantyl)-4-bromo-1-decyloxy benzene

To a suspension of sodium hydride (80% in oil, 3.2 g, 104 mmol) in 100 ml of THF, there is slowly added a solution of 2-(1-adamantyl)-4-bromophenol (29 g, 95 mmol) in 200 ml of THF. The mixture is stirred until the evolution of gas ceases at which point 27.8 g (23 ml, 104 mmol) of 1-iododecane and 100 ml of DMF are added. The mixture it stirred for 12 hours at ambient temperature, poured into water, extracted with ether, dried and the solvents evaporated. The resulting residue is pruified by passage through a silica column (eluant: heptane), yielding 40.7 g (96%) of 2(1-adamantyl)-4-bromo-1-decyloxybenzene. Melting point: 69°–70° C.

(b) Methyl ester of 6-3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid

In a manner analogous to Example 9c, starting with 17.9 g (40 mmol) of the brominated derivative obtained in part (a) above, and 5.3 g of methyl 6-bromo-2-naphthoate, 7.4 g (67%) of the expected ester are obtained. Melting point: 113°–114° C.

EXAMPLE 15

6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—$OC_{10}H_{21}$ and R_1=COOH

6.3 g (11 mmol) of the ester obtained in Example 14 dissolved in 200 ml of THF are treated at reflux with 200 ml of 2M methanolic soda for 4 hours. The solvents are evaporated and the residue is taken up in water, acidified to pH 1 (concentrated HCl), filtered, washed with water and the solid is extracted with ether. The extract is dried and the solvent evaporated. The resulting residue is treated with 700 ml of ethyl acetate at reflux. On cooling 5.9 g (97%) of the expected acid are obtained. Melting point: 214°–215° C.

EXAMPLE 16

Methyl ester of 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—OC_6H_{13} and R_1=—$COOCH_3$

5.3 g (13 mmol) of the ester obtained in Example 12 are dissolved in 100 ml of DMF and added to a suspension of NaH (80% in oil; 0.46 g; 15.4 mmol) in DMF (50 ml). The mixture is stirred at ambient temperature until the evolution of gas ceases, at which point 1-iodohexane (3.26 g; 2.3 ml; 15.4 mmol) is added. This mixture is then stirred for 4 hours at ambient temperature, poured into water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column (eluant: mixture of dichloromethane—50% and hexane—50%), then recrystallized in isooctane to give 5.5 g (87%) of the expected pure product. Melting point: 129°–130° C.

EXAMPLE 17

6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=—OC_6H_{13} and R_1=—COOH

In a manner analogous to Example 15, starting with 4.2 g (8.4 mmol) of the ester obtained in Example 16, 3.8 g (95%) of 6-[(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 260°–261° C.

EXAMPLE 18

Methyl ester of 6-[3- (1-adamantyl)-4-methoxy phenyl]-4-acetoxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=—$OCOCH_3$, R_2=1-adamantyl, R_3=—OCH_3 and R_1=—$COOCH_3$

47.6 g (148 mmol) of 2-(1-adamantyl)-4-bromoanisole and 13.9 g (6.3 ml, 74 mmol) of dibromoethane, dissolved in 100 ml of THF are added slowly to a suspension of magnesium (5.4 g, 222 mmol) in the THF (1000 ml). The mixture is brought to reflux for 2 hours at which point zinc chloride (20.2 g, 148 mmol) is added. The mixture is stirred for 1 hour and there are successively added 2.9 g (74 mmol) of methyl 4-acetoxy-6-bromo-1-methyl-2-naphthoate and 500 mg of $NiCl_2$/DPPE complex. This mixture is stirred for 8 hours at ambient temperature, poured into a saturated aqueous solution of ammonium chloride, extracted with CH_2Cl_2, dried and the solvents evaporated. The resulting residue is purified by passage through a silica column (eluant: mixture of hexane, 40%, and CH_2Cl_2, 60%). The resulting product is recrystallized in isopropyl ether, yielding 23.5 g (64%) of the expected ester. Melting point: 201°–202° C.

EXAMPLE 19

6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=OH, R_2=1-adamantyl, R_3=OCH_3 and R_1=COOH

23 g (46 mmol) of the ester obtained in Example 18 are treated at reflux for 12 hours with 300 ml of methanolic soda (2N). The solvents are evaporated and the residue is taken up in water and acidified to pH 1 (concentrated HCl). The solid is filtered, washed with water, dissolved in ethyl ether, dried ($MgSO_4$) and evapo-

rated. The resulting residue is recrystallized in ethyl acetate to give 18.7 g (92%) of the expected acid. Melting point: 281°–283° C.

EXAMPLE 20

Methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid Compound of Formula I wherein R_4=CH_3, R_5=OH, R_2=1-adamantyl, R_3=OCH_3 and R_1=$COOCH_3$

17 g (38 mmol) of the acid obtained in Example 19 are treated for 12 hours at reflux with 200 ml of methanol containing 2 ml of sulfuric acid. The solvents are evaporated and the residue is taken up in water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column using as the eluant a 90:10 mixture of ether/THF. The product is recrystallized in ethyl acetate to obtain the expected pure ester—15 g (86%). Melting point: 272°–274° C.

EXAMPLE 21

Methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1 =—$COOCH_3$

(a) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethylaminothiocarbonyloxy-1-methyl-2-naphthoate

4.56 g of the ester obtained in Example 20, dissolved in THF (100 ml) are slowly added to a suspension of sodium hydride (80% in oil, 360 mg, 12 mmol) in DMF (50 ml). The mixture is stirred for 1 hour at ambient temperature and then for 1 hour at 40° C. There are then added 1.75 g (14 mmol) of dimethylthiocarbamoyl chloride, and the mixture is stirred initially at ambient temperature for 2 hours and then at 40° C. for 2 hours. The reaction mixture is poured into water, extracted with ether, dried, and the solvents evaporated. The product is purified by passage through a silica column (eluant: CH_2Cl_2), yielding 4 g (74%) of the expected intermediate product. Melting point: 137°–138° C.

(b) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethyl-carbonythio-1-methyl-2-naphthoate

3.8 g (7 mmol) of the ester obtained above in part (a) are heated under nitrogen at 260° C. for 0.5 hour. The residue is taken up in methylene chloride and purified by passage through a silica column (eluant: CH_2Cl_2). The resulting gum is taken up in isopropyl ether, yielding 3.3 g (87%) of the desired intermediate. Melting point: 201°–202° C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid

The intermediate obtained above in part (b)—(11 g, 20 mmol) is dissolved in 500 ml of ethanol. 20 g of Raney nickel are added and the reaction mixture is heated at reflux for 4 hours. 20 g of nickel are then added and the mixture is heated again for 1 hour, at which point the mixture is cooled, concentrated and taken up in CH_2Cl_2 (1000 ml). The precipitate is filtered and the filtrate is recovered, dried and evaporated. The product is purified by passage through a silica column (eluant: CH_2Cl_2) and recrystallized in a mixture of ethyl acetate (90%) and THF (10%), yielding 8 g (90%) of the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Melting point: 238°–239° C.

EXAMPLE 22

6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein R_4=CH_3, R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1=COOH.

6.8 g (15.4 mmol) of the ester obtained in Example 21(c) are treated as in Example 10 to give 5.8 g (88%) of the corresponding acid. Melting point: 300°–302° C.

EXAMPLE 23

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthalene methanol. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1=—CH_2OH

1.3 g (3 mmol) of the ester obtained in Example 9 dissolved in THF (5 ml) are treated with 171 mg (4.5 mmol) of $LiAlH_4$. The mixture is heated at reflux, cooled and treated with a saturated aqueous solution of the double tartrate of sodium and potassium. The reaction mixture is filtered, evaporated to dryness, and the residue is recrystallized in cyclohexane, yielding 1.0 g (83%) of the 6-13-(1-adamantyl)-4-methoxyphenyl]-2-naphthalene methanol. Melting point: 163°–164° C.

EXAMPLE 24

Ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=1-adamantyl, R_3=OCH_3 and R_1=—$CONHC_2H_5$

(a) 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid chloride

4.75 g (1.15 mmol) of the acid obtained in Example 10 in 200 ml of dichloromethane are treated with 2.08 g (2.3 ml, 1.15 mmol) of dicyclohexamine. The mixture is stirred at ambient temperature until dissolution. The solvents are evaporated and the residue taken up in ether. The solid thus formed is filtered (6.8 g) and then taken up in methylene chloride (50 ml). 1.37 g (0.84 ml, 1.15 mmol) of thionyl chloride are added. The salt formed is filtered and the filtrate is recovered, evaporated and dried. The resulting solid (3.9 g) is used as such in the following step.

(b) Ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-b 2-naphthoic acid

1.3 g (3 mmol) of the acid chloride produced in (a) above are dissolved in 20 ml of THF. 405 mg (600 µl, 9 mmol) of ethylamine are added and the mixture is stirred for 2 hours at ambient temperature. The mixture is then poured into water, extracted with CH_2Cl_2, dried and evaporated. The residue is recrystallized in ethyl acetate, yielding 1.1 g (85%) of the expected ethylamide. Melting point: 220°–221° C.

EXAMPLE 25

Morpholide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

In a manner analogous to Example 24, starting with 1.3 g of acid chloride produced in part (a) of Example 24 and 780 mg (780 ml, 9 mmol) of morpholine, there

are obtained 1.3 g (91%) of the expected morpholide. Melting point: 212°-213° C.

EXAMPLE 26

Methyl ester of 6-3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein R'_2=tert.butyl, R'_3=R'_6=OCH_3

(a) 4-bromo-2-tert.butyl anisole

3.10 g (22.6 mmol) of aluminum chloride are added all at once to a mixture of 63.5 g (339 mmol) of p-bromoanisole and 31.4 g (330 mmol) of tert.butyl chloride. The mixture is stirred at ambient temperature until the evolution of gas ceases (about 15 minutes). The mixture is then heated at 80° C. for 15 minutes and poured into ice. 300 ml of water are added and the mixture is extracted with ether.

The organic phase is dried ($MgSO_4$), the solvents evaporated and the residue purified by chromatography on a silica column (eluant: mixture of methylene chloride—10% and hexane—90%). After evaporation of the solvents, 4-bromo-2-tert.butyl anisole under the form of a colorless oil which crystallized on cooling is obtained. 31.9 g (39%).

(b) Methyl ester of 6-3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid

There is slowly added, drop by drop, a solution of 18.8 g (77 mmol) of 4-bromo-2-tert.butyl anisole to 2.26 g (93 mmol) of magnesium turnings and a crystal of iodine. The mixture is heated until the Grignard begins to form, at which point the remainder of the solution containing the brominated derivative is poured in a manner to maintain a regular reflux. Once the addition is complete, the mixture is heated at 40° C. for 30 minutes, diluted with 200 ml of THF and cooled to ambient temperature. 12.7 g (93 mmol) of dry zinc chloride in solution in 20 ml of THF are added and the mixture is stirred for 30 minutes at ambient temperature. There are then successively added 12.1 g (46 mmol) of methyl 6-bromo-2-naphthoate and 300 mg of $NiCl_2$/DPPE complex.

The mixture is stirred for 10 hours at ambient temperature. 300 ml of water are added and the THF is evaporated. The remainder is extracted with methylene chloride. The organic phase is dried ($MgSO_4$), filtered, evaporated and purified by passage through a silica column (eluant: mixture of 50% dichloromethane and 50% hexane). After evaporation of the solvents, the resulting residue is recrystallized in hexane to give the expected ester: 11.5 g (72%). Melting point-160° C.

EXAMPLE 27

6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid. Compound of Formula II wherein R'_2=tert.butyl, R'_3=OCH_3 and R'_6=OH.

In a manner analogous to Example 15, starting with 7.0 g (20 mmol of the ester obtained in Example 26, 6.0 g (90%) of the expected acid are obtained. Melting point: 268° C.

EXAMPLE 28

Methyl ester of 6[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=$C(CH_3)_2C_9H_{19}$, R_3=OCH_3 and R_1=—$COOCH_3$

A solution of 16 g (45 mmol) of 2- (1,1-dimethyldecyl)-4-bromo anisole in 60 ml of THF is slowly added to 1.3 g (54 mmol) of magnesium and a crystal of iodine. The mixture is slightly heated at the beginning of the addition until the reaction of formation of the Grignard is initiated. Then the remainder of the solution containing the brominated derivative is added in a manner to maintain a regular reflux. Once the addition is complete, the mixture is stirred for 30 minutes at 50° C. and then cooled to ambient temperature. 7.4 g (54 mmol) of zinc chloride in solution in 50 ml of THF are added. The mixture is stirred for 30 minutes at ambient temperature, 6.6 g (25 mmol) of methyl 6-bromo-2-naphthoate are added and then 175 mg of $NiCl_2$/DPPE complex. The mixture is stirred for 3 hours at ambient temperature at which point 250 ml of water are added. The THF is evaporated under reduced pressure and the residue is extracted with dichloromethane, dried and the solvent eva-porated. The residue is purified by passage through a silica column (eluant: mixture of 60% dichloromethane and 40% hexane). On evaporation, a solid is obtained which is recrystallized twice in hexane to give the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid: 7.05 g (61%). Melting point: 92° C.

EXAMPLE 29

6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein R_4=R_5=H, R_2=$C(CH_3)_2C_9H_{19}$, R_3=OCH_3 and R_1=COOH.

In a manner analogous to Example 15, starting with 3.6 g of the ester obtained in Example 28, 3 (87%) of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid are obtained. Melting point: 180° C.

Examples of Compositions

Example A

Fatty cream wherein the active principle is in suspension

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid	0.001 g
A combination of nonionic E/H emulsifiers and a fatty body of mineral origin sold by Goldschmidt under the trade name "Protegin X"	25.00 g
Petrolatum oil	10.00 g
Preservatives, sufficient amount	
Water, sufficient amount for	100.00 g

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxy phenyl]-1-methyl 2-2-naphthoic acid.

Example B

Skin cream—A fluid cream wherein the active principle is in suspension

Methyl ester of 6-(4-tert.butyl phenyl)-2-naphthoic acid	0.02 g
Sorbitan stearate polyoxyethylenated with 20 moles of ethylene oxide sold by Atlas under the trade name "Tween 60"	5.00 g
Sorbitan monostearate sold by Atlas under the trade name "Span 60"	2.00 g
Cetyl alcohol	5.00 g
Triglycerides of capric and caprylic acids sold by Dynamit Nobel under the trade name "Miglyol 812"	10.00 g

-continued

Preservatives, sufficient amount	
Water, sufficient amount for	100.00 g

Example C

Gel for the skin or scalp wherein the active principle is in suspension

Methyl ester of 6-(4-t.butyl phenyl)-2-naphthoic acid	0.10 g
Ethanol	20.00 g
Hydroxypropyl cellulose, sold by Hercules under the trade name "Klucel HF"	2.00 g
Preservative, sufficient amount	
Water, sufficient amount for	100.00 g

Example D

Lotion for the skin

6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid	0.1 g
Polyethylene glycol 400	70.0 g
Ethanol	29.9 g

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Example E

Unguent for the skin

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid	0.001 g
Lanolin	50 g
Vaseline, sufficient amount for	100 g

Example F

Oral composition—0.30 g gelule

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid	0.003 g
Cornstarch	0.060 g
Lactose, sufficient amount for	0.300 g

The resulting powder is packaged in a gelule whose wall is made of gelatin, TiO_2 and a preservative.

Example G

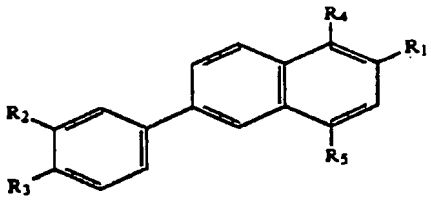
Capsule containing 0.400 g of the following suspension

Ethylamide of 6-[3-(1-adamantyl)-4-methoxy-phenyl]-2-naphthoic acid	0.005 g
Glycerine	0.200 g
Sucrose	0.050 g
Polyethylene glycol 400	0.050 g
Purified water, sufficient amount for	0.400 g

This suspension is packaged in a capsule made of gelatin, glycerine titanium dioxide and water.

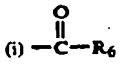
What is claimed is:

1. A process for the treatment of a dermatologic, rheumatismal, respiratory or ophtalmologic disease comprising administering to a person suffering from said disease an effective amount of a composition containing, in a pharmaceutically acceptable vehicle, as the active ingredient thereof a benzonaphthalene compound of the formula



wherein

R_1 represents



or (ii) $—CH_2OH$,

R_6 represents

or OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

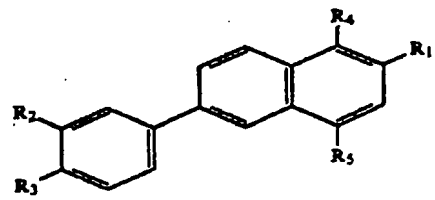
R_2 represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical,

R_3 represents hydrogen, hydroxy, branched or straight chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical selected from the group consisting of 1-methylcyclohexyl and 1-adamantyl, a thiocycloaliphatic radical, or $—O—Si(CH_3)_2—R_8$ wherein R_8 represents linear or branched alkyl,

R_4 and R_5 each independently represent hydrogen, lower alkyl or lower acyloxy.

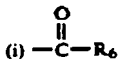
or a salt thereof.

2. A cosmetic composition for body and hair hygiene comprising a cosmetically acceptable vehicle and an effective amount of as the active ingredient at least one benzonaphthalene compound of the formula



wherein

R_1 represents



or (ii) $-CH_2OH$,

R_6 represents

or OR_7 wherein R_7 represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

R_2 represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical,

R_3 represents hydrogen, hydroxy, branched or straight chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical selected from the group consisting of 1-methylcyclohexyl and 1-adamantyl, a thiocycloaliphatic radical, or $-O-Si(CH_3)_2-R_8$ wherein R_8 represents linear or branched alkyl,

R_4 and R_5 each independently represent hydrogen, lower alkyl or lower acyloxy,

or a salt thereof.

3. The cosmetic composition of claim 2 wherein said active ingredient is present in an amount ranging from 0.0005 to 2 weight percent based on the total weight of said composition.

4. The cosmetic composition of claim 2 wherein said active ingredient is present in an amount ranging from 0.01 to 1 weight percent based on the total weight of said composition.

* * * * *

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	RE 34,440	183	960	----	07/913,897	11/09/93	07/16/92	04	ND	PAID
	(5,098,895)				(07/502,122)	(03/24/92)	(03/30/90)			PAID

If the "status" column for a patent number listed above does not indicate "PAID" a codeor an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set outbelow by the related item number. An explanation of the codes indicated in the "status" column and as et out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	6183

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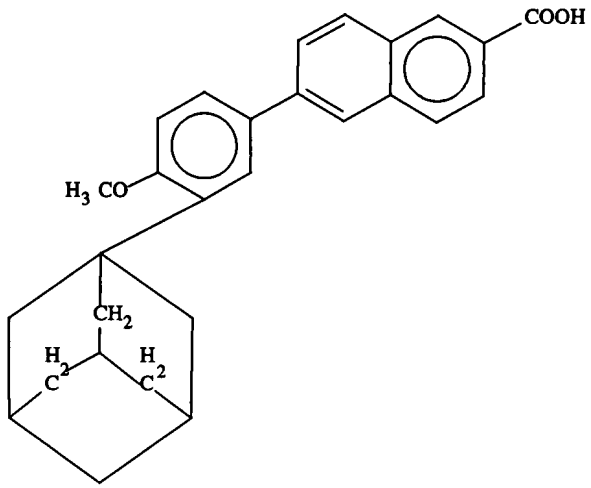
PTOL-439 (REV. 8-88)

APPENDIX C



Adapalene

****
*** ACTIVITY REPORT ***
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TO: Karen Tyson

FROM: Donna M. Meuth

DATE: September 11, 1996

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Re: Patent Term Extension Applications for U.S. Patent Nos. RE 34,440 and 4,717,720

As per your request, attached are copies of the Patent Office stamped postcard receipts dated July 26, 1996, for the above-identified application.

Client No. 010095.003 Fax Tel. No. 308-6916

If you have any questions regarding compatibility, you may reach our Office Services Department at (703) 836-6620.

Appln. for Ext. of Patent Term
Declaration & ck/ $1,060.00

PAPER

INVENTOR Shroot et al

SERIAL NO. USP 4,717,720

FILING DATE Issued 1/5/88

RECEIVED BY THE UNITED STATES PATENT OFFICE

010095-003a Galderma DMM 7/26/96

Paper: Appln. for Ext. of Patent Term Declaration & ck. $1,080.00

Inventor(s): Shroot et al

Patent No.: Re. 34,440

Issue Date: 11/9/93

Received by the United States Patent Office

010095-003d Galderma DMM July 26, 1996